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Cross-cultural Cognitive Assessment of Dementia: A Meta-analysis of the Impact of Illiteracy on Dementia Screening and an Evaluation of a Transcultural Short-term Memory Assessment

Caragh Maher

Doctorate in Clinical Psychology

The University of Edinburgh

May 2021

Acknowledgements

First and foremost, I would like to thank my supervisor, Dr Clara Calia, for her support, guidance and enthusiasm throughout this process. When the Covid-19 pandemic meant that my initial project was no longer viable, Clara was quick to provide support and help me move onto plan B! I could not have asked for a kinder supervisor.

I would also like to thank Dr Angus Lorimer, who provided encouragement and practical support during the early stages of my project. A special thanks also to Dr Mario Parra for sharing his expertise to help me gain a deeper understanding of the thesis topic.

Thank you to my family for their unwavering belief in me and their support since day one - none of this would have been possible without you.

To my fellow trainees, and particularly my Aberdream gang, thank you so much for all the laughs and emotional support throughout the doctorate.

Finally, a special thanks to Maurice Johnson, who fostered my interest in learning and academia in my school days. I am forever grateful for his encouragement (and kind references!).

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Total word count excluding references and appendices: 21,253

Thesis abstract

Introduction: A major challenge in detecting dementia is that many of the tools used to screen for dementia are affected by linguistic, cultural, and educational factors. As the prevalence of dementia is expected to rise, exploring suitable methods of assessing dementia in diverse populations is becoming increasingly important.

Aims: The first aim of this thesis was to assess research on dementia screening tools in literate and illiterate individuals to evaluate the impact of illiteracy on these tools, through a systematic review and meta-analysis. The second aim was to assess the predictive ability and construct validity of the Visual Short-Term Memory Binding Task (VSTMBT), a proposed transcultural tool.

Methods: A systematic review identified 37 studies, 27 of which were included in a meta-analysis. In addition, data from a longitudinal study, which involved assessing older adults at three time points over two years, were examined. Data were collected from 72 healthy control participants and 82 participants with a diagnosis of Mild Cognitive Impairment (MCI). Linear mixed models and logistic regression models were used to assess how well the VSTMBT and other baseline measures of cognition predicted future cognitive decline and the development of Alzheimer's Disease (AD). Finally, partial correlations between baseline neuropsychological assessments were conducted to examine the construct validity of the VSTMBT.

Results: In the meta-analysis, multi-level random effects models revealed that literate participants had a significant advantage over illiterate participants in dementia screening tools. In the longitudinal study, the VSTMBT did not significantly predict cognitive decline or conversion from MCI to AD. Partial correlation analyses showed that the VSTMBT did not significantly correlate with other measures of memory and failed to discriminate between measures of executive function, processing speed and visuospatial ability.

Conclusions: The meta-analysis highlighted the unsuitability of traditional dementia screening tools for individuals who are illiterate, emphasising the need for the screening tools that consider varying levels of literacy. The results of the longitudinal study were in line with the idea that the VSTMBT has higher predictive value at the preclinical stage compared to the MCI stage of AD. This study highlighted the need for different cognitive tests at different stages of AD progression.

Lay Summary

The purpose of cognitive testing is to assess memory, learning, and thinking skills. Cognitive tests usually involve written and spoken tasks designed to measure these skills. They are used in the process of diagnosing dementia.

These tests differ all over the world, depending on the country and culture in which they were developed. That is because the culture we are in and the type of education that we receive affects how we learn and think.

Many of the tools used are only suitable for people from a Western culture who are able to read and write proficiently. This is a problem, because the prevalence of dementia is rising across the world, and particularly in non-Western, low-income countries where there are high rates of illiteracy.

This thesis contains two papers. The first paper focused on reviewing previous research examining the difference between literate and illiterate older adults in terms of their performance in cognitive tests. The second paper focused on a specific cognitive test called the Visual Short-Term Memory Binding Task (VSTMBT). Previous studies have shown that the VSTMBT is unaffected by culture and education. The aim of this study was to check whether the VSTMBT can predict future decline in memory, learning, and thinking skills, and whether it can predict future dementia. We also wanted to examine whether the VSTMBT was an accurate measure of short-term memory.

In the first paper, we found 37 studies reporting cognitive test scores in literate and illiterate older adults. Results from 27 of these studies were synthesised and we found that literate individuals had a significant advantage over illiterate individuals in most cognitive tests.

For the second paper, we looked at data from a study that involved assessing 154 older adults at three time points over two years. Approximately half of these participants were healthy, and the other half had mild impairments in memory, learning, and thinking. We found that the VSTMBT was not very good at predicting future decline or at predicting dementia in this group of people. We think that this might because, by the time people have mild – but noticeable - impairments, it's too late to test them using the VSTMBT because by then, their performance in the task is too poor. In order to be an accurate predictor, we think we need to test people with the VSTMBT long before they show any signs of dementia. We also found that people's performance in VSTMBT did not relate to their performance in other more traditional tools. We think this might be because the VSTMBT measures a very specific type of memory function that other tools do not measure.

Overall, both of these papers highlight the importance of carrying out further research on the development of cognitive tests that are suitable for people of all abilities and can predict dementia before it becomes symptomatic.

1 The effect of illiteracy on performance in screening tools for dementia: a systematic review and meta-analysis

Caragh Maher[a] & Clara Calia[a]

[a] *Clinical and Health Psychology, School of Health in Social Science, University of Edinburgh, Edinburgh, EH8 9AG, UK*

Corresponding author: Caragh Maher

Manuscript prepared for submission to Journal of Neuropsychology (https://bpspsychub.onlinelibrary.wiley.com/journal/17486653). Journal guidelines are included in Appendix A

Total word count excluding references: 9,171

Word count excluding abstract, reference list, tables and figures, in line with journal guidelines (max 6,000): 5,661

1.1 Abstract

Research indicates that many tools designed for screening dementia are affected by literacy level. The objective of this study was to estimate the overall effects of this important confounding factor. A systematic review and a meta-analysis were conducted to evaluate differences in performance in dementia screening tools between literate and illiterate individuals.

Electronic databases were searched from 1975 to June 2021 to identify empirical studies examining performance in dementia screening tools in literate and illiterate individuals over 50 years old. Data for effect sizes, participant demographic information, and study information were extracted.

We identified 37 studies collectively comprising of 29,073 individuals classified as literate and 16,455 individuals classified as illiterate. Twenty-seven studies were methodologically suitable for meta-analysis. Multi-level random-effects modelling demonstrated a significant overall effect, with literate participants scoring significantly higher than illiterate participants (g =, -1.2098, *95% CI* = -1.4696, -0.9500, $p < 0.001$). Moderator analyses indicated significant effects of test type and the presence of cognitive impairment on the extent of the difference in performance between literate and illiterate participants. The difference in performance between groups was smaller in screening tests modified for illiterate individuals ($p < 0.01$), and in individuals with cognitive impairment ($p < 0.001$).

Our findings substantiate the unsuitability of many dementia screening tools for individuals who are illiterate. The results of this systematic review and meta-analysis emphasise the need for the development and validation of tools that are suitable for individuals of all abilities.

1.2 Introduction

1.2.1 Literacy

Despite advances in the provision of education in recent decades, a significant proportion of the world's population still lack basic literacy skills. In 2019, UNESCO reported that approximately 9% (102 million) of young people and 14% (750 million) of adults are illiterate (UIS, 2019). Elderly illiteracy rates are higher still, with 22% (141 million) of adults over 65 unable to read or write (UIS, 2017).

The definition of literacy is ambiguous, with no clear cut-off point. For this reason, subcategories of literacy are often characterised, including semi-literacy and functional literacy (Ardila et al., 2010). UNESCO's simplest definition characterises literacy as the ability to read and write, with understanding, a short simple statement about one's everyday life (UNESCO, 1978). However, the organisation recognises the need to shift from defining literacy as a dichotomous variable (literate versus illiterate) to a more nuanced description of levels of proficiency and functionality (Bokova, 2012). The Organisation for Economic Co-operation and Development (OECD) provides a more complex definition, whereby literacy is defined as "the ability to understand, evaluate, use and engage with written texts to participate in society, to achieve one's goals, and to develop one's knowledge and potential" (OECD, 2013, p. 59). Despite this shift towards nuance, however, in most countries, and particularly in lower-income countries, reporting of literacy rates is still limited to the traditional dichotomy of literate versus illiterate (UIS, 2019).

The main reasons for illiteracy can be broadly divided into two categories: reasons pertaining to health or to social circumstances. Health reasons for illiteracy include learning difficulty or disability and physical or neurological conditions. Social reasons include the absence of an education system, social or cultural disapproval of literacy, child labour, and poverty (Ardila et al., 2010). It should be noted that, although literacy is highly related to schooling, reading and writing skills can be obtained outside of education. It cannot be assumed, therefore, that an individual who did not attend formal education is illiterate (Ardila & Rosselli, 2007).

1.2.2 Dementia and illiteracy

Assessment of dementia in individuals who are illiterate is complex. It has been shown that individuals who are illiterate are significantly more likely to receive a diagnosis of dementia (Herrera, Caramelli, Silveira, & Nitrini, 2002; Nitrini et al., 2009). There are numerous potential explanations for this.

One possible explanation relates to brain development. The acquisition of literacy skills affects the functional and structural development of the brain (Ardila et al., 2010). The cognitive reserve hypothesis proposes that the neural networks in the brains of illiterate individuals may be more susceptible to disruption or may struggle to compensate for cognitive dysfunction (Manly, Touradji, Tang, & Stern, 2003). This theory is debated within the field of cross-cultural neuropsychology, however, as many have argued that it fails to adequately consider potential confounds, such as testing bias (Ardila et al., 2010; Ostrosky-Solis, 2007).

Traditional tests used to screen for and diagnose dementia were not developed for individuals who are unable to read or write (Ardila & Rosselli, 2007). Screening tests, such as the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), assess specific skills that are enhanced by the process of learning to read (Ostrosky-Solis, 2007). For example, learning to read trains remembering strategies, visuospatial perception, logical reasoning, and fine movements. Individuals who are illiterate often possess a different skill set, one that is more procedural, pragmatic and sensory oriented. However, these skills are less likely to be tested in the process of cognitive assessment. Thus, individuals who are illiterate are at a disadvantage when assessed in the cognitive domains that benefit from literacy skills, even when assessment of these domains does not directly involve reading or writing (Kosmidis, 2018; Ostrosky-Solis, 2007).

Furthermore, individuals who are illiterate usually lack familiarity with testing procedures. People who go through an education system are socialised into a value system which places importance on working alone, memorisation, and doing your best to succeed without any obvious immediate benefit to your daily functioning (Nell, 2000). These values may not be held by individuals who did not go through such a system. Thus, differences in performance in cognitive tests may not be completely reflective of differences in cognitive ability, but rather differences in test-taking abilities and familiarity.

1.2.3 Dementia screening tools

The MMSE is one of the most frequently used screening tools for dementia across the globe, both in research and in clinical practice. However, many studies have demonstrated that the MMSE is affected by educational level, language of administration, and culture (e.g., Black et al., 1999; Goudsmit et al., 2018; Nielsen, Vogel, Gade, & Waldemar, 2012). Studies have attempted to account for some of these confounds by lowering the cut-off score for some populations (Black et al., 1999; Cassimiro, Fuentes, Nitrini, & Yassuda, 2017). Brucki, Nitrini, Caramelli, Bertolucci, and Okamoto (2003) proposed cut-off points, calculated by taking the mean score minus one standard deviation for different education levels. Using this formula, a cut-off score of <17/18 (compared to the standard <24) is commonly used for populations with low education to indicate probable dementia (Cassimiro et al., 2017; Leite, Miotto, Nitrini, & Yassuda, 2017). However, evidence suggests that while modifying the cut-off score in the MMSE may increase specificity, it reduces sensitivity (Ostrosky-Solis, 2007).

In light of this evidence, a number of alternative tools have been developed, such as the Literacy Independent Cognitive Assessment (LICA; Choi et al., 2011), the Community Screening Instrument for Dementia (CSI-D; Hall et al., 2000), the Rowland Universal Dementia Assessment Scale (RUDAS; Storey, Rowland, Conforti, & Dickson, 2004), and the European Cross-Cultural Neuropsychology Test Battery (Nielsen et al., 2018). These tools were designed for use in multicultural and illiterate/low educated populations. They differ from traditional tools largely by having more of a focus on abilities acquired in everyday life (e.g., experience with shopping for groceries) rather than relying on school-dependent skills and abilities (Nielsen, 2018).

1.2.4 Rationale and objective

The number of individuals living with dementia across the globe is estimated to increase from 50 million in 2018 to 152 million in 2050, a 204% increase (WHO, 2019). The reasons for this increase are complex and include factors such as increased life expectancy, improvements in the reporting of health data, and an increase in knowledge about dementia (Alzheimer's Research UK, 2018).

The prevalence of dementia in low-income countries is currently lower than in high income countries because the life expectancy is lower. As life expectancy increases in low-income countries, so too will the prevalence of dementia. The most drastic increase in the number of people living with dementia is therefore estimated to occur in low-income countries (Prince et al., 2015). The lowest literacy rates are also in these countries (UIS, 2019). Finding accurate and appropriate methods of diagnosing dementia in individuals who are illiterate is therefore increasingly relevant. In order to inform the development and promotion of such methods, it is important to understand the extent to which the current methods of screening dementia are affected by illiteracy.

This review aims to identify, evaluate and summarise the findings of all studies exploring how illiterate individuals perform in dementia screening tools compared to literate individuals. To our knowledge, this is the first systematic review on this topic. This review will make the available evidence more accessible to researchers and policy makers. It is anticipated that this work will help guide future research on the topic and assist in the promotion of accessible diagnostic tools.

1.3 Methods

1.3.1 Search criteria

The systematic review and meta-analysis were carried out using PRISMA guidelines (Liberati et al., 2009). The PRISMA checklist is included in Appendix B. The protocol for the review was registered on PROSPERO, with following reference number: CRD42020168484 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=168484).

A comprehensive search was conducted on 24th June 2021 using OVID databases (MEDLINE, PsycINFO, and EMBASE), Scopus, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Google Scholar from 1975 (year of publication of the MMSE; Folstein et al., 1975) to June 2021. The search strategy included combinations of the following phrases:

(dement OR "cognitive impairment" OR "alzheimer*") AND (screening OR mmse OR "mini mental" OR "moca" or "montreal cognitive assessment" OR "GPCOG" OR "General Practitioner Assessment of Cognition" OR "mini-cog" OR "mini cog" OR "addenbrooke's cognitive assessment" OR "ace-r" OR "ace-iii") AND (literate OR illiterate OR literacy OR illiteracy OR "reading abilit*" OR "reading comprehension").*

1.3.2 Eligibility criteria

Studies that met the following criteria were included in the systematic review:

1. Quantitative study
2. Measured performance of literate and illiterate adults over 50 years old in a dementia screening tool. Although most studies on dementia focus on participants over 65 years, it is recognised that dementia also affects people under the age of 65 (van der Flier & Scheltens, 2005). Many research studies reflect this in their age criteria (e.g., Goudsmit et al., 2020; Muangpaisan, Assantachai, Sitthichai, Richardson, & Brayne, 2015; Nielsen, 2018; Zhou et al., 2006). In order avoid a potential cultural bias towards studies conducted in countries whereby 65 years old is deemed the cut-off for older age, an inclusive age range was chosen.
3. Illiterate participants were illiterate for social reasons (e.g., poverty, lack of education, culture group). Only studies that explicitly stated that participants were illiterate were included; participants with no education were not assumed to be illiterate. Studies that included participants who were illiterate as a result of health conditions (e.g., learning disability, motor/sensory/neurological conditions) were excluded.
4. Published in English in a peer-reviewed journal

Studies were included in the meta-analysis if they reported sufficient information to allow for the calculation of the effect size and standard error of difference in performance between the two groups (literate vs. illiterate adults) in the screening tool. Where sufficient information was not available, authors were contacted to request the required data.

1.3.3 Data extraction

Relevant data were extracted from the studies by the lead author using Microsoft Excel. The extracted data included the year, study design, screening tool used, language of administration, study country, sample size, age range, gender breakdown, cognitive impairment diagnosis, years of education, primary findings, statistical analysis used, and the mean and standard deviation of performance in the cognitive screening tool in literate and illiterate participants.

1.3.4 Quality assessment

The lead author assessed the quality of all included studies, and a random 50% of the papers were assessed by an independent researcher to ensure reliability (kappa = 0.83, indicating near perfect agreement). Disagreements were resolved by consensus. Study quality was assessed using the National Institutes of Health (NIH) Quality Assessment of Case-Control Studies tool (National Institutes of Health, 2014). The NIH Quality Assessment of Case-Control Studies tool does not include specific rules for calculating the quality of the studies. As a general guideline, studies that met 8 or more of the criteria were graded as good, those that met between 6 and 7 of the criteria were graded as fair, and those that met 5 of less of the criteria were graded as poor.

Of the 12 questions in the tool, two questions were excluded, as they were not relevant to the studies in this review. The question regarding concurrent controls was excluded because 'cases' in this review referred to illiterate individuals. Illiterate participants did not become illiterate at a specific moment in time, therefore making it impossible to select concurrent control participants. The question regarding confirming exposure prior to the development of the condition that defined a participant as a case was also excluded for the same reason. The condition that defined a participant as a 'case' was illiteracy, which did not develop over time.

Studies were not excluded from the systematic review on the basis of quality. However, studies with a quality rating of 'poor' due to unclear selection of participants or ambiguous differentiation of literate and illiterate participants were excluded from the meta-analysis. As the methods used to delineate the number of participants in each group were questionable in these studies, they were excluded from the quantitative analysis to reduce the risk of bias across the studies.

1.3.5 Statistical analyses

Analyses and plots were carried out in RStudio (V1.3.959; RStudio Team, 2020), using R packages 'meta' (Balduzzi, Rücker, & Schwarzer, 2019), 'metafor' (Viechtbauer, 2010), and 'ggplot2' (Wickham, 2016) . The effect sizes of interest were those obtained from comparisons of independent groups (literate vs. illiterate) in terms of cognitive screening test scores. Studies that reported mean scores and standard deviations were included in the meta-analysis, and effect sizes were calculated as Hedges' *g*.

A multi-level random-effects model was used to weight studies and calculate a summary effect size. A random-effects model was chosen to take into consideration the fact that differences in sample size may create variations in effect sizes across studies. A multi-level model was used to account for dependence within the data. Meta-analytic pooling assumes statistical independence. If there is dependency between effect sizes, this may result in false-positive results. Where authors assess more than one screening tool within the same study, the effect sizes calculated for each tool are not independent (Harrer, Cuijpers, Furukawa, & Ebert, 2019). Thus, these effect sizes cannot be added to a meta-analytic model without accounting for their dependency. A multi-level model takes these dependencies into account by adding another layer into the structure of the meta-analytic model. This allows the model to account for the fact that some effect sizes are nested within one study. In the present analysis, a three-level model was implemented to model sampling variation for each effect size (Level 1), variation within each study (Level 2), and variation between studies (Level 3; Cheung, 2014; Harrer et al., 2019).

Summary effects were calculated using the restricted maximum likelihood (REML) method. Standard errors and 95% confidence intervals were calculated for each effect size. *P*-values were calculated to test the null hypotheses and *Q* and I_2 statistics were used to assess heterogeneity and observed variance respectively. Publication bias and outlier biases were analysed using a funnel plot and asymmetry was tested statistically using Egger's regression test (Egger, Davey Smith, Schneider, & Minder, 1997). To maintain independence, average study effect sizes were used in the funnel plot and in Egger's regression test.

The main analyses examined the overall difference in performance in cognitive screening tests between literate and illiterate groups. A sensitivity analysis was carried out to assess whether the results differed across studies with different primary aims. To assess this, studies were divided into one of three groups depending on the objectives of the study. The first group included studies that focused on examining the difference in performance between literate and illiterate participants as their primary research question. The second group included studies that focused on this comparison as a secondary research question. The third group included studies that provided data on cognitive test scores for literate and illiterate participants but did not explicitly compare groups.

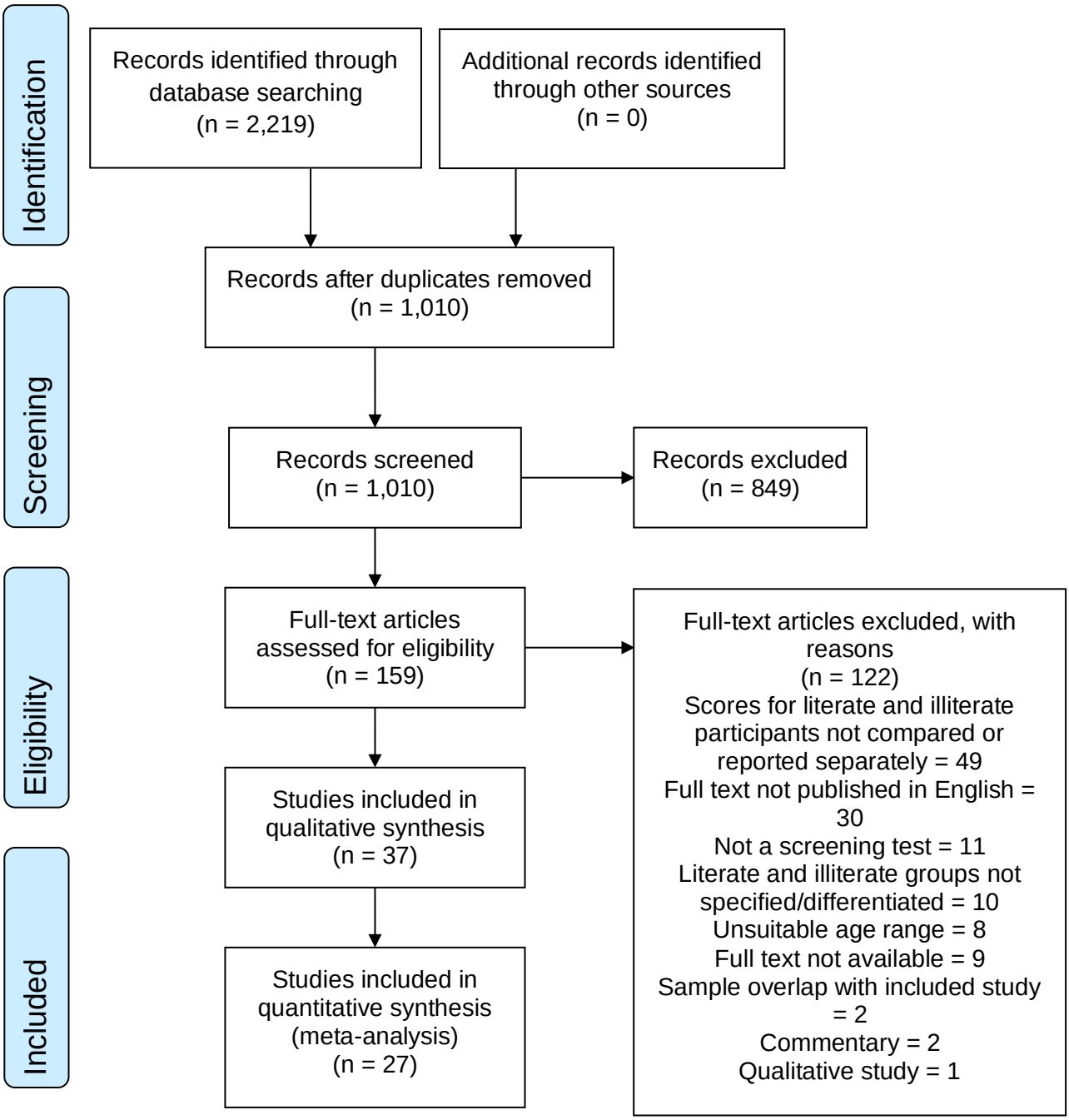
Moderator analyses were carried out to assess whether the type of cognitive screening test or cognitive status affect the results of the main analysis. Cognitive screening tests were categorised by whether or not they were designed or modified for individuals with low levels of literacy or education. To assess whether cognitive status impacted on the results, participants were categorised as healthy, as having mild cognitive impairment, or as having dementia.

1.4 Results

1.4.1 Results of systematic search

The results of the systematic search are summarised in Figure 1.1. The search yielded 2,219 studies. After removing duplicates, the titles and abstracts of the remaining 1,010 studies were screened and 849 records were excluded. A total of 159 manuscripts were retrieved and the full texts were assessed for eligibility. Of these records, 122 were excluded, with reasons outlined in Figure 1.1. Reasons for exclusion for each article excluded at full-text review are outlined in Appendix C. Thirty-seven studies were identified as meeting the inclusion criteria and were therefore included in the systematic review.

Figure 1.1: PRISMA flow diagram of the study selection process



1.4.2 Study characteristics

The main characteristics of the included studies are summarised in Table 1.1. The studies collectively comprised of 45,528 participants, with study sample sizes ranging from 34 to 16,488. Of these participants, 16,455 individuals were identified as illiterate, and 29,073 individuals were classified as literate. The gender breakdown of the collective sample was 59% female (*n* = 26,763) and 40% male (*n* = 18,005). Three studies, with 618 total participants, did not report the participants' gender.

Seventeen studies either focused on healthy older adults only or did not report the cognitive status of the participants. Twenty studies included both healthy and cognitively impaired older adults. In these 20 studies, 27,207 individuals were identified as healthy, 750 were classified as having MCI or possible dementia, and 2,382 were reported to have dementia or probable dementia.

The majority of the studies (33 of 37 studies) included the MMSE or an adapted version of the MMSE as a cognitive screening tool. Eleven studies included a cognitive screening tool that was adapted for use in illiterate/low educated participants. The studies were carried out in 13 different countries and included cognitive screening tools administered in 10 different languages. The most common language was Portuguese (11 studies), followed by Korean (6 studies), Chinese (4 studies), and Hindi (4 studies). Only 2 studies administered screening tools in English and both of these studies were carried out in the USA.

Table 1.1: Characteristics of included studies

Authors (Year)	Location of study (Language)	Sample size (n) (Illiterate/ Literate)	Age (M(SD) unless otherwise specified)	Gender (n)	Education (n, unless otherwise specified)	Cognitive status (n)	Screening tool(s) assessed	Relevant findings
Arguvanli et al. (2015)	Turkey (Turkish)	900 (Illiterate: 311 Literate: 589)	71.6 (0.2)	Female: 431 Male: 469	Illiterate: 311 Literate: 156 ≥5y: 433	Not reported	MMSE	The study found a significant relationship between cognitive status based on MMSE score (<24/25 & >24/25) and literacy status (illiterate / literate / >5 years education)
Balduino et al. (2020)	Brazil (Portuguese)	143 (Illiterate: 23 Literate: 120)	85.85 (4.73)	Not reported	Illiterate: 23 1-4y: 77 >4y: 44	All healthy	MMSE CAMCOG CDT	Scores varied significantly according to education level, such that illiterate participants scored lower than literate participants in the MMSE, CAMCOG, and CDT
Black et al. (1999)	USA (Spanish/ English)	2,853 (Illiterate: 546 Literate: 2307)	*n per age group* 65-69y: 1145 70-74y: 765 75-79y: 464 ≥80y: 479	Female: 1662 Male: 1191	0: 506 1-8y: 1886 9-11y: 185 ≥12y: 276	Not reported	MMSE	Illiterate participants scored significantly lower than literate participants.
Brito-Marques & Cabral-Filho (2004)	Brazil (Portuguese)	232 (Illiterate: 28 Literate: 204)	69.4 (6.8)	Not reported	Illiterate: 28 1-4y: 119 5-8: 85	Not reported	MMSE-mo MMSE-ad	Scores varied significantly according to education level, such that illiterate participants scored lower than literate participants in both the MMSE-mo and the MMSE-ad
Caramelli et al. (2007)	Brazil (Portuguese)	205 (Illiterate: 52 Literate: 153)	76.5 (6.6)	Female: 141 Male: 64	Illiterate: 52 1-3y: 46 4-7y: 60 ≥8y: 47	Healthy: 117 Dementia: 88	MMSE	No statistical comparison between literate and illiterate participants. Data extracted for meta-analysis only.

Authors (Year)	Location of study (Language)	Sample size (n) (Illiterate/ Literate)	Age (M(SD) unless otherwise specified)	Gender (n)	Education (n, unless otherwise specified)	Cognitive status (n)	Screening tool(s) assessed	Relevant findings
Cassimiro et al. (2017)	Brazil (Portuguese)	164 (Illiterate: 60 Literate: 104)	*Median (IR)* Illiterate: 70 (67-73) 1-2y: 69 (68-72.5) 3-4y: 70 (66.5-73)	All female	Illiterate: 60 1-2y: 52 3-4y: 52	Not reported	MMSE	Scores varied significantly according to education level, such that illiterate participants scored lower than literate participants.
Cesar et al. (2017)	Brazil (Portuguese)	623 (Illiterate: 86 Literate: 537)	*n per age group* 60-69y: 304 70-79y: 215 ≥80: 104	Female: 393 Male: 230	0: 86 1-3y: 180 4-7y: 213 8-11y: 83 ≥12y: 61	Healthy: 385 Cognitive impairment no dementia: 135 Dementia: 110	ACE-R MMSE	Scores varied significantly according to education level, such that illiterate participants scored lower than literate participants in both the ACE-R and the MMSE
Contador et al. (2017)	Spain (Spanish)	3,816 (Illiterate: 481 Literate: 3,335)	73.8 (6.6)	Female: 2,148 Male: 1,668	Illiterate: 481 Ability to read/write: 1,614 Primary school: 1,251 Secondary school: 470	Healthy: 3,654 Dementia: 162	MMSE-37	Illiterate participants scored significantly lower than literate participants
Devraj et al. (2014)	India (Hindi)	270 (Illiterate: 63 Literate: 207)	67.5 (5.8)	Female: 81 Male: 189	Illiterate: 63 Primary: 68 Secondary: 77 Graduation & above: 62	Not reported	HMSE	Illiterate participants scored significantly lower than literate participants
Elbedewy & Elokl (2020)	Egypt (Arabic)	143 (Illiterate: 72 Literate: 71)	67.17 (5.41)	Female: 81 Male: 62	Illiterate: 72 Education: 71	Healthy:73 MCI: 70	MMSE CDT	Scores did not vary significantly according to literacy, gender or cognitive status. Illiterate and literate participants were not directly

Authors (Year)	Location of study (Language)	Sample size (n) (Illiterate/ Literate)	Age (M(SD) unless otherwise specified)	Gender (n)	Education (n, unless otherwise specified)	Cognitive status (n)	Screening tool(s) assessed	Relevant findings
								compared independently of gender/cognitive status.
Gambhir et al. (2014)	India (Hindi)	728 (Illiterate: 635 Literate: 93)	65.7 (5.8)	Female: 469 Male: 259	Not reported	Healthy: 708 Dementia: 20	HMSE	Illiterate participants scored significantly lower than literate participants
Goudsmit et al. (2020)	The Netherlands (Native language using interpreter. Majority Turkish/ Arabic)	129 (Illiterate: 67 Literate: 62)	*Median (IR)* Community controls: 68 (63–74) Patients, intact cognition: 76 (70–78) MCI: 77 (71–82) Dementia: 78 (74–81)	Female: 80 Male: 49	No education: 74 Primary: 38 Secondary: 14 Tertiary: 3	Healthy: 47 MCI: 33 Dementia: 49	MMSE RUDAS	Illiterate participants scored significantly lower than literate participants in the MMSE. There was no difference between groups in the RUDAS.
Hamrick et al. (2013)	USA (English)	219 (Illiterate: 74 Literate: 145)	80 (7)	Not reported	<High school: 111 High school: 108	Healthy: 62 Cognitive impairment : 157	M-MMSE	No statistical comparison between literate and illiterate participants. Data extracted for meta-analysis only.
Hong et al. (2011)	Korea (Korean)	125 (Illiterate: 36 Literate: 89)	74.9 (6.05)	Female: 75 Male: 50	Uneducated illiterate: mean 0y ± 0y Uneducated literate: mean 0.5y ± 0y Educated literate: mean 8.8y ± 4.1y	All healthy	K-MMSE	Scores varied significantly according to education level, such that illiterate participants scored lower than literate participants
Julayanont et al. (2015)	Thailand (Thai)	85 (Illiterate: 28 Literate: 57)	68.4 (6.8)	Female: 71 Male: 14	*M(SD)* = 3.2y (1.6y)	Healthy: 43 Mild cognitive impairment : 42	MMSE MOCA-B	No statistical comparison between literate and illiterate participants. Data extracted for meta-analysis only.

Authors (Year)	Location of study (Language)	Sample size (n) (Illiterate/ Literate)	Age (M(SD) unless otherwise specified)	Gender (n)	Education (n, unless otherwise specified)	Cognitive status (n)	Screening tool(s) assessed	Relevant findings
Katzman et al. (1988)	China (Chinese)	5,030 (Illiterate: 1,350 Literate: 3,680)	*n per age group* 55-64y: 1496 65-74y: 2180 75y+: 1354	Female: 2825 Male: 2205	Illiterate: 1,350 Elementary: 1,853 Middle school: 1,827	Not reported	CMMS	No statistical comparison between literate and illiterate participants. Data extracted for meta-analysis only.
Kim & Chey (2010)	Korea (Korean)	240 (Illiterate: 28 Literate: 212)	69.1 (8.1)	Female: 166 Male: 74	Illiterate: 28 0y: 18 1-6y: 72 ≥7: 122	Healthy: 240 (Dementia: 28 - not included in analysis)	CDT	Scores varied significantly according to literacy status, such that illiterate participants scored lower than literate participants.
Kim et al. (2014)	Korea (Korean)	203 (Illiterate: 29 Literate: 174)	74 (6.9)	Female: 139 Male: 64	Pure illiterate: 29 Semi illiterate: 67 Literate: 75 High-level literate: 32	All healthy	MMSE	Scores varied significantly according to education level, such that illiterate participants scored lower than literate participants
Kochhann et al. (2010)	Brazil (Portuguese)	968 (Illiterate: 72 Literate: 896)	70.6 (7.3)	Female: 633 Male: 335	Illiterate: 72 Lower education: 415 Middle education: 277 Higher education: 204	Healthy: 806 Dementia: 162	MMSE	No statistical comparison between literate and illiterate participants. Data extracted for meta-analysis only.
Leite et al. (2017)	Brazil (Portuguese)	180 (Illiterate: 60 Literate: 120)	74.9 (7.1)	Female: 139 Male: 41	Illiterate: 60 1-2y: 60 3-4y: 60	All healthy	MMSE	Scores varied significantly according to education level, such that illiterate participants scored lower than literate participants
Lenardt et al. (2009)	Brazil (Portuguese)	33 (Illiterate: 22 Literate: 11)	79.82 (8.23)	All female	Illiterate: 22 3-10y: 9 >10y: 2	Healthy: 24 Cognitive decline: 9	MMSE	No statistical comparison between literate and illiterate participants. Data extracted for meta-analysis only.

Authors (Year)	Location of study (Language)	Sample size (n) (Illiterate/ Literate)	Age (M(SD) unless otherwise specified)	Gender (n)	Education (n, unless otherwise specified)	Cognitive status (n)	Screening tool(s) assessed	Relevant findings
Lin et al. (2002)	Taiwan (Chinese)	2,096 (Illiterate: 843 Literate: 1,253)	76.1 (6.3)	Female: 1,037 Male: 1,059	0y: 843 1-5y: 330 ≥6: 923	Healthy: 1,178 Dementia: 918	CASI-C 2.0	In healthy participants, scores varied significantly according to education level, such that illiterate participants scored lower than literate participants. Data for participants with dementia was not reported.
Mokri et al. (2012)	Mexico (Spanish)	167 (Illiterate: 101 Literate: 66)	80.85 (7.55)	Not reported for those with MMSE scores	All 0y education	Not reported	MMSE	Illiterate participants scored significantly lower than literate participants
Muangpaisan et al. (2015)	Thailand (Thai)	4,459 (Illiterate: 348 Literate: 4,111)	64.2 (7.9)	Female: 3,195 Male: 1,264	0y: 349 Study as monk: 9 1-4y: 2619 Primary school: 319 Secondary school: 892 Bachelor degree or higher: 271	All healthy	TMSE	Illiterate participants scored significantly lower than literate participants in each domain in the TMSE except the registration domain.
Nielsen (2018)	Denmark (Danish/ Turkish)	41 (Illiterate: 20 Literate: 21)	62.9 (8.0)	Female: 31 Male: 10	Illiterate group: 0y Literate group: *M(SD)* = 4.4y (2.3y)	Not reported	RUDAS	There was no difference between the scores of literate and illiterate participants.
Nitrini et al. (2004)	Brazil (Portuguese)	51 (Illiterate: 23 Literate: 28)	73.8 (5.4)	Female: 24 Male: 27	Illiterate group: 0y Literate group: *M(SD)* = 3.8y (3.3y)	All healthy	MMSE CDT	Illiterate participants scored significantly lower than literate participants in both the MMSE and the CDT

Authors (Year)	Location of study (Language)	Sample size (n) (Illiterate/ Literate)	Age (M(SD) unless otherwise specified)	Gender (n)	Education (n, unless otherwise specified)	Cognitive status (n)	Screening tool(s) assessed	Relevant findings
Ortega et al. (2021)	Brazil (Portuguese)	117 (Illiterate: 48 Literate: 69)	76.4 (6.9)	Female: 72 Male: 45	Illiterate group: 0y Literate group: mean 2.9y ± 1.1y	Healthy: 69 Dementia: 48	MMSE CDT	No statistical comparison between literate and illiterate participants in the MMSE. Data extracted for meta-analysis only. Illiterate control participants scored significantly lower than literate control participants in the CDT
Paddick et al. (2014)	Tanzania (Swahili)	1,186 (Illiterate: 617 Literate: 569)	Not reported	Female: 668 Male: 518	No school: 585 School: 601	Healthy: 910 Possible dementia: 104 Probable dementia: 184	CSI-D	Illiterate participants scored significantly lower than literate participants.
Park et al. (2014)	Korea (Korean)	80 (Illiterate: 40 Literate: 40)	74.6 (6.6)	Female: 67 Male: 13	Mean 3.94y ± 4.93y	Healthy: 40 Dementia: 40	MMSE	Healthy illiterate participants scored significantly lower than healthy literate participants. Illiterate participants with dementia scored significantly lower than literate participants with dementia.
Scazufca et al. (2009)	Brazil (Portuguese)	1,933 (Illiterate: 744 Literate: 1,189)	72.2 (6.2)	Female: 1,172 Male: 761	0y: 744 ≥1y: 1,189	Healthy: 1,849 Dementia: 84	MMSE	Illiterate participants scored significantly lower than literate participants.
Shim et al. (2015)	Korea (Korean)	762 (Illiterate: 140 Literate: 622)	72.2 (6.6)	Female: 474 Male: 288	*M(SD)* = 6.5y (5.13y)	Healthy: 634 Mild cognitive impairment : 128	K-MMSE LICA	No statistical comparison between literate and illiterate participants. Data extracted for meta-analysis only.

Authors (Year)	Location of study (Language)	Sample size (n) (Illiterate/ Literate)	Age (M(SD) unless otherwise specified)	Gender (n)	Education (n, unless otherwise specified)	Cognitive status (n)	Screening tool(s) assessed	Relevant findings
Subramanian et al. (2021)	India (Hindi)	240 (Illiterate: 93 Literate: 147)	63.9 (7.1)	Female: 150 Male: 90	Illiterate: 93 Primary: 64 Middle: 47 High school and above: 36	Healthy: 168 Mild cognitive impairment: 40 Moderate cognitive impairment: 31 Severe cognitive impairment: 1	HMSE	The study found a significant relationship between cognitive status based on HMSE score (<26 & >26) and literacy status (illiterate / literate)
Tiwari et al. (2009)	India (Hindi)	40 (Illiterate: 20 Literate: 20)	*n per age group* 60-74y: 34 ≥75y: 6	Female: 12 Male: 28	Illiterate: 20 ≥5y: 20	Not reported	HMSE HVMMSE	The study found a significant relationship between cognitive status based on HVMMSE score (<23 & >23) and literacy status (illiterate / literate). No significant relationship was found between cognitive status based on HMSE score (<19 & >19) and literacy status (illiterate / literate)
Umakalyani & Senthilkumar (2018)	India (local native language)	109 (Illiterate: 32 Literate: 77)	68.25 (6.4)	Female: 58 Male: 51	*Illiterate: 32* *Literate: 77*	Not reported	MMSE	Illiterate participants scored significantly lower than literate participants
Xu et al. (2003)	China (Chinese)	370 (Illiterate: 74 Literate: 444)	70.23 (6.76)	Female: 158 Male: 212	*M(SD)* = 4.4y (2.8y)	Healthy: 277 Dementia: 93	CAMSE	Healthy illiterate participants scored significantly lower than healthy literate participants. There was no difference between illiterate and literate participants with dementia.

Authors (Year)	Location of study (Language)	Sample size (n) (Illiterate/ Literate)	Age (M(SD) unless otherwise specified)	Gender (n)	Education (n, unless otherwise specified)	Cognitive status (n)	Screening tool(s) assessed	Relevant findings
Youn et al. (2011)	Korea (Korean)	100 (Illiterate: 50 Literate: 50)	73.2 (6.0)	All female	Illiterate group: 0y Literate group: *M(SD)* = 7.5y (2.4y)	Healthy: 50 Dementia: 50	MMSE	Healthy illiterate participants scored significantly lower than healthy literate participants. There was no difference between illiterate healthy participants and literate participants with AD.
Zhou et al. (2006)	China (Chinese)	16,488 (Illiterate: 9,130 Literate: 7,358)	63.4 (7.6)	Female: 9,813 Male: 6,675	Illiterate: 9,130 1-6y: 6,092 >6y: 1,266	Healthy: 16,114 Dementia: 374	mCMMSE	Scores varied significantly according to education level, such that illiterate participants scored lower than literate participants.

Abbreviations:

n: number of participants
M: Mean
SD: Standard Deviation
y: years

ACE-R: Addenbrooke's Cognitive Examination-Revised
CAMCOG: Cambridge Cognition Examination
CAMSE: Chinese adapted Mini-Mental State Examination
CASI-C 2.0: Cognitive Abilities Screening Instrument, Chinese version
CDT: Clock Drawing Test
CMMS: Chinese Mini-Mental Status
CSI-D: Community Screening Instrument for Dementia
HMSE: Hindi Mini-Mental State Examination
HVMMSE: Hindi version Mini-Mental State Examination
K-MMSE: Korean Mini-Mental State Examination
LICA: Literacy Independent Cognitive Assessment
M-MMSE: Modified Mini-Mental State Examination
mCMMSE: Modified Chinese Mini-Mental State Examination
MMSE-37: 37-point version of Mini-Mental State Examination
MMSE-ad: Mini-Mental State Examination adapted
MMSE-mo: Mini-Mental State Examination modified
MMSE: Mini-Mental State Examination
MOCA-B: Montreal Cognitive Assessment-Basic
RUDAS: Rowland Universal Dementia Assessment Scale
TMSE: Thai Mini-Mental State Examination

1.4.3 Study quality

Quality assessment ratings for all included studies are outlined in Table 1.2. Seven studies were rated as good, 21 as fair, and 8 as poor. All but 3 studies (Devraj et al., 2014; Lin et al., 2002, Subramanian et al., 2021) clearly defined the aims of the study, and all studies clearly defined the study population. Only two studies provided a justification for the sample size (Arguvanli et al., 2015; Elbedewy & Elokl, 2020). No study explicitly outlined whether the researchers were blinded to the participants' literacy status. However, it is likely that maintaining blindedness during the process of cognitive assessment would have been difficult. Confounders were adjusted for in the analyses of 19 studies.

Table 1.2: Quality assessment ratings based on the NIH Quality Assessment of Case-Control Studies tool

Study	Overall rating	Clearly defined aim	Clearly defined study population	Sample size justified	Cases & controls from similar popula-tion	Con-sistent inclusion/ exclusion criteria	Cases & controls clearly differen-tiated	Random selection from eligible partici-pants	Measures defined and valid	Blinding	Con-founders adjusted
Arguvanli et al. (2015)	Fair	Yes	Yes	Yes	Yes	Yes	No	CD	Yes	NR	Yes
Balduino et al. (2020)	Fair	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	No
Black et al. (1999)	Fair	Yes	Yes	No	Yes	CD	No	NA	Yes	NR	Yes
Brito-Marques & Cabral-Filho (2004)	Good	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	Yes
Caramelli et al. (2007)	Fair	Yes	Yes	No	Yes	CD	No	NA	Yes	NR	NA
Cassimiro et al. (2017)	Fair	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	No
Cesar et al. (2017)	Fair	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	No
Contador et al. (2017)	Fair	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	No
Devraj et al. (2014)	Poor	No	Yes	No	Yes	CD	CD	Yes	Yes	NR	No
Elbedewy & Elokl (2020)	Good	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NR	Yes
Gambhir et al. (2014)	Poor	Yes	Yes	No	Yes	CD	No	NA	Yes	NR	No
Goudsmit et al. (2020)	Fair	Yes	Yes	No	Yes	Yes	Yes	No	Yes	NR	Yes
Hamrick et al. (2013)	Good	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	Yes
Hong et al. (2011)	Poor	Yes	Yes	No	Yes	Yes	Yes	CD	CD	NR	No
Julayanont et al. (2015)	Poor	Yes	Yes	No	Yes	CD	CD	NA	CD	NR	Yes
Katzman et al. (1988)	Good	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	Yes
Kim et al. (2010)	Good	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	Yes
Kim et al. (2014)	Fair	Yes	Yes	No	Yes	CD	Yes	NA	Yes	NR	Yes
Kochhann et al. (2010)	Fair	Yes	Yes	No	Yes	CD	CD	NA	Yes	NR	Yes
Leite et al. (2017)	Fair	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	No
Lenardt et al. (2009)	Fair	Yes	Yes	No	Yes	Yes	No	NA	Yes	NR	No
Lin et al. (2002)	Poor	No	Yes	No	No	CD	No	NA	Yes	NR	Yes
Mokri et al. (2012)	Fair	Yes	Yes	No	Yes	CD	Yes	NA	Yes	NR	Yes
Muangpaisan et al. (2015)	Fair	Yes	Yes	No	Yes	CD	No	NA	Yes	NR	Yes
Nielsen (2018)	Fair	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	No
Nitrini et al. (2004)	Fair	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	No
Ortega et al. (2021)	Fair	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	No
Paddick et al. (2014)	Good	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	Yes
Park et al. (2014)	Good	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	Yes
Scazufca et al. (2009)	Poor	Yes	Yes	No	Yes	CD	No	NA	Yes	NR	No
Shim et al. (2015)	Good	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	Yes
Subramanian et al. (2021)	Fair	No	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes

Tiwari et al. (2009)	Poor	Yes	Yes	No	Yes	CD	Yes	No	Yes	NR	No
Umakalyani et al. (2018)	Poor	Yes	Yes	No	Yes	Yes	No	CD	CD	NR	No
Xu et al. (2003)	Fair	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	No
Youn et al. (2011)	Fair	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NR	No
Zhou et al. (2006)	Fair	Yes	Yes	No	Yes	CD	Yes	NA	Yes	NR	Yes

Abbreviations: NA = Not Applicable, NR = Not Reported, CD = Cannot Determine
Scoring: Good: ≥8 Yes/NA Fair: 6-7 Yes/NA Poor: ≤5 Yes/NA

1.4.4 Qualitative synthesis

Seven studies collected and reported data for literate and illiterate participants but did not carry out a statistical comparison between the two groups (Caramelli, Carthery-Goulart, Porto, Charchat-Fichman, & Nitrini, 2007; Hamrick, Hafiz, & Cummings, 2013; Julayanont et al., 2015; Katzman et al., 1988; Kochhann, Varela, Lisboa, & Chaves, 2010; Lenardt et al., 2009; Shim et al., 2015). These studies provided sufficient data to be included in the meta-analysis but as the results presented in these studies do not directly relate to the research question of this review, they will not be discussed qualitatively.

In 17 of the remaining 30 studies, examining the difference in performance between literate and illiterate participants was the primary research question. In the other 13 studies, this was a secondary research question, with six validation studies, four prevalence studies, two studies designed to obtain norms or cut-off scores, and one assessing factors that contribute to cognitive impairment.

In 28 of these 30 studies, the results demonstrated that illiterate participants scored significantly lower than literate participants in at least one cognitive screening test. Only four studies reported finding no significant difference between literate and illiterate participants in terms of their scores in a cognitive screening tool. Both Goudsmit et al. (2020) and Nielsen (2018) demonstrated that literate and illiterate participants performed similarly in the RUDAS, and Tiwari, Tripathi, and Kumar (2009) reported no significant difference in performance in the Hindi Mini-Mental State Examination (HMSE) in literate and illiterate participants. Both the RUDAS and the HMSE were designed to minimize the effect of literacy ability and educational attainment on performance. Elbedewy & Elokl (2020) found that scores in the MMSE or CDT did not vary significantly according to literacy, gender, or cognitive status but did not directly compare literate and illiterate participants independently of gender and cognitive status. Nine other studies included screening tools that were designed or modified to consider low literacy or education levels. However, each of these studies reported significant differences between literate and illiterate participants in terms of their performance in these tools.

Where studies included participants with diagnosed cognitive impairment or dementia, there was variety across the studies with regards to how this information was used in the analyses. Seven studies did not report screening scores separately according to diagnosis (Contador et al., 2017; Gambhir, Khurana, Kishore, Sinha, & Mohapatra, 2014; Goudsmit et al., 2020; Lenardt et al., 2009; Paddick et al., 2014; Subramanian et al., 2021; Zhou et al., 2006). Four studies found significant differences in test performance between healthy literate and illiterate participants but did not report differences between literate and illiterate participants with dementia (Lin et al., 2002; Scazufca, Almeida, Vallada, Tasse, & Menezes, 2009; Xu et al., 2003; Youn et al., 2011). Youn et al. (2011) also found that healthy illiterate participants performed similarly to literate participants with dementia. Cesar, Yassuda, Porto, Brucki, and Nitrini (2017) found that performance in the Addenbrooke's Cognitive Examination-Revised (ACE-R) differed according to education level in healthy participants, participants with cognitive impairment, and participants with dementia.

1.4.5 Meta-analysis

1.4.5.1 Study selection and characteristics

Seven studies did not include sufficient data for inclusion in the meta-analysis. The authors of 6 of these studies were contacted. The authors of one study (Devraj et al., 2014) could not be contacted because there were no author contact details specified in the paper. Two authors replied and provided the necessary data for the meta-analysis (Cassimiro et al., 2017; Goudsmit et al., 2020). Five studies were given a quality rating of 'poor' and were therefore excluded from the meta-analysis (Devraj et al., 2014; Gambhir et al., 2014; Hong et al., 2011; Julayanont et al., 2015, Umakalyani & Senthilkumar, 2018). The final number of studies included in the meta-analysis was 27.

1.4.5.2 Cognitive screening scores in literate vs. illiterate older adults

Effect sizes were calculated for the differences in performance in cognitive screening tests between the literate groups and illiterate groups. A significant overall effect was found, with literate participants scoring significantly higher than illiterate participants (g =, -1.2098, *95% CI* = [-1.4696, -0.9500], $p < 0.001$; Table 1.3; Figure 1.2). However, significant heterogeneity was found ($Q = 591.37$, $p < 0.001$, $I^2 = 98.05\%$). There were no distinct outliers, so all studies were included. No statistically significant asymmetry was observed from funnel plots (see Figure 1.3) using Egger's test ($p = 0.52$).

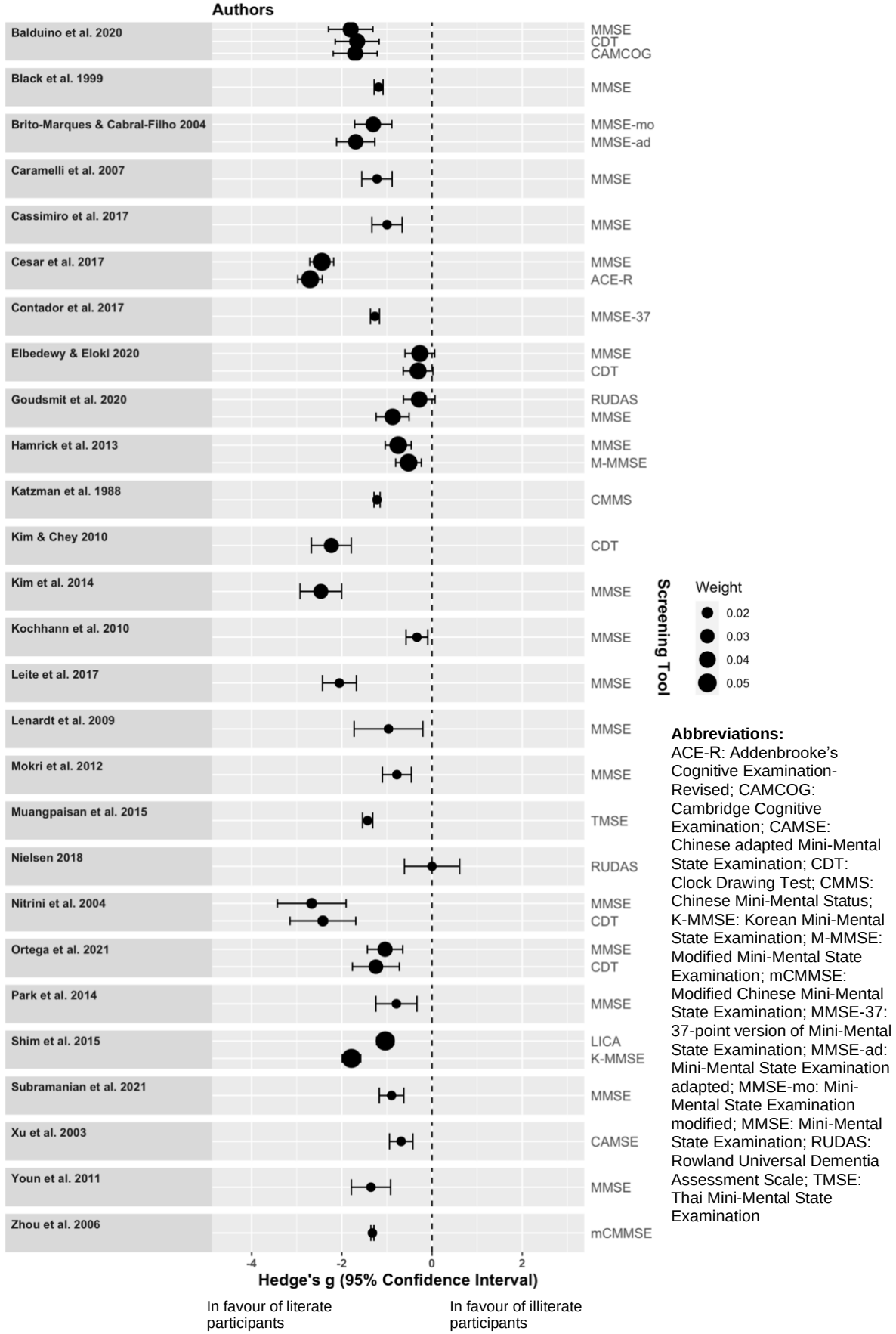
Table 1.3: Results from the multi-level random-effects model

Study	Screening tool	Hedges' g	Lower CI	Upper CI	Weight (random)
Balduino et al. 2020	MMSE	-1.1847	-1.2829	-1.0864	1.41%
Balduino et al. 2020	CAMCOG	-1.3028	-1.7154	-0.8903	3.43%
Balduino et al. 2020	CDT	-1.6931	-2.1173	-1.269	3.42%
Black et al. 1999	MMSE	-1.2207	-1.5569	-0.8845	1.32%
Brito-Marques & Cabral-Filho 2004	MMSE-mo	-0.9975	-1.3333	-0.6618	1.32%
Brito-Marques & Cabral-Filho 2004	MMSE-ad	-2.705	-2.9778	-2.4322	4.64%
Caramelli et al. 2007	MMSE	-2.4462	-2.7113	-2.181	4.65%
Cassimrio et al. 2007	MMSE	-1.2659	-1.3656	-1.1662	1.41%
Cesar et al. 2017	ACE-R	-0.8739	-1.2397	-0.5082	3.87%
Cesar et al. 2017	MMSE	-0.2844	-0.6355	0.0666	3.89%
Contador et al. 2017	MMSE-37	-0.521	-0.8053	-0.2368	4.49%
Elbedewy & Elokl 2020	MMSE	-0.7492	-1.0379	-0.4605	4.48%
Elbedewy & Elokl 2020	CDT	-1.2188	-1.2856	-1.1521	1.41%
Goudsmit et al. 2020	MMSE	-2.2334	-2.6755	-1.7912	3.21%
Goudsmit et al. 2020	RUDAS	-0.3353	-0.5759	-0.0948	1.37%
Hamrick et al. 2013	M-MMSE	-2.0535	-2.4295	-1.6774	1.30%
Hamrick et al. 2013	MMSE	-1.4283	-1.5416	-1.3149	1.41%
Katzman et al. 1988	CMMS	0	-0.6124	0.6124	1.15%
Kim & Chey 2010	CDT	-2.4205	-3.1497	-1.6912	1.84%
Kim et al. 2014	MMSE	-2.668	-3.4301	-1.9059	1.80%
Kochhann et al. 2010	MMSE	-1.7862	-1.9904	-1.5821	5.26%
Leite et al. 2017	MMSE	-1.0373	-1.2279	-0.8467	5.28%
Lenardt et al. 2009	MMSE	-0.6846	-0.9441	-0.4251	1.36%
Mokri et al. 2012	MMSE	-1.3542	-1.7895	-0.919	1.27%
Muangpaisan et al. 2015	TMSE	-1.3217	-1.3555	-1.2878	1.42%
Nielsen et al. 2018	RUDAS	-1.804	-2.2972	-1.3109	3.62%
Nitrini et al. 2004	CDT	-1.7033	-2.1915	-1.215	3.64%
Nitrini et al. 2004	MMSE	-1.6598	-2.1461	-1.1736	3.65%
Ortega et al. 2021	MMSE	-0.2695	-0.5988	0.0598	4.12%
Ortega et al. 2021	CDT	-0.3095	-0.6393	0.0203	4.12%
Park et al. 2014	MMSE	-2.4656	-2.9266	-2.0046	3.18%
Shim et al. 2015	K-MMSE	-0.9649	-1.727	-0.2028	1.04%
Shim et al. 2015	LICA	-0.779	-1.1004	-0.4577	1.33%
Subramanian et al. 2021	MMSE	-1.0411	-1.4332	-0.649	3.25%
Xu et al. 2003	CAMSE	-1.2448	-1.7651	-0.7245	3.04%

Youn et al. 2011	MMSE	-0.79	-1.2454	-0.3347	1.25%
Zhou et al. 2006	mCMMSE	-0.8971	-1.169	-0.6252	1.35%
Multi-level random effects model		-1.2098	-1.4696	-0.9500	**100%**

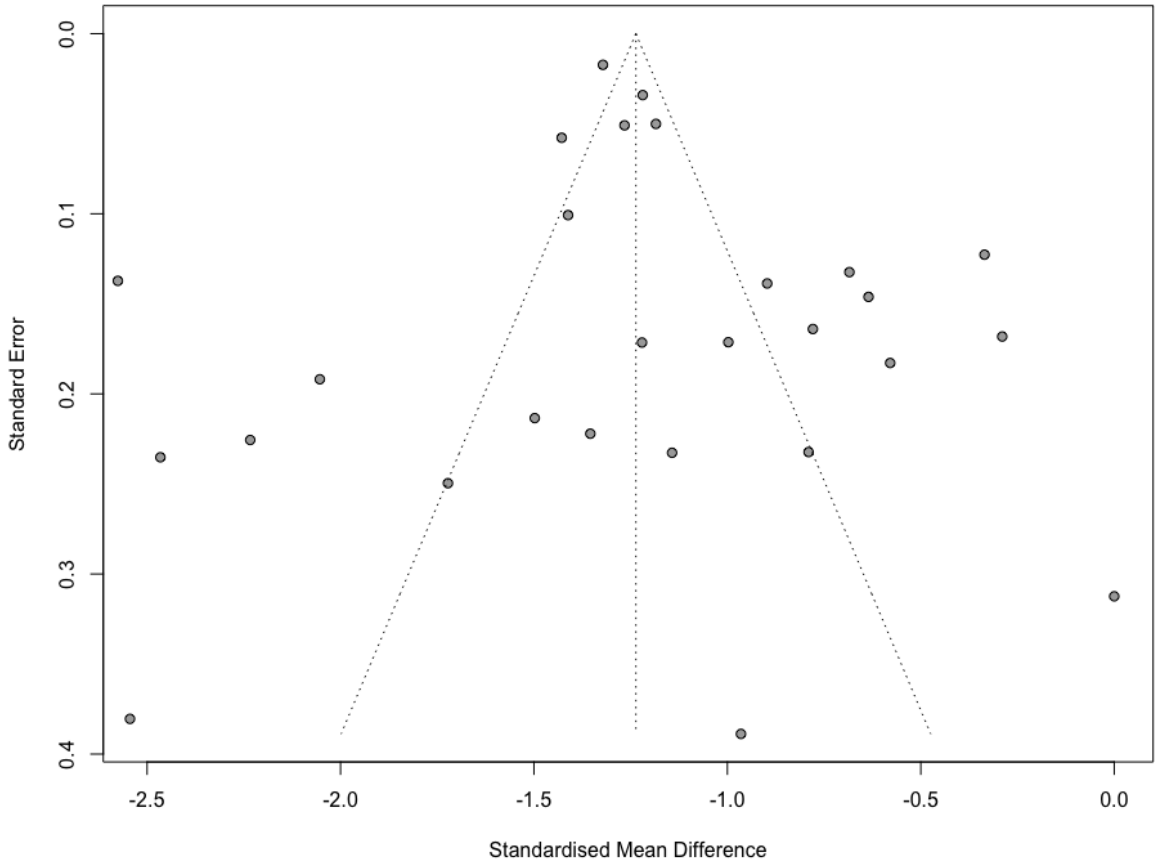
Abbreviations: CI = confidence interval; ACE-R: Addenbrooke's Cognitive Examination-Revised; CAMSE: Chinese adapted Mini-Mental State Examination; CAMCOG: Cambridge Cognition Examination; CDT: Clock Drawing Test; CMMS: Chinese Mini-Mental Status; K-MMSE: Korean Mini-Mental State Examination; M-MMSE: Modified Mini-Mental State Examination; mCMMSE: Modified Chinese Mini-Mental State Examination; MMSE-37: 37-point version of Mini-Mental State Examination; MMSE-ad: Mini-Mental State Examination adapted; MMSE-mo: Mini-Mental State Examination modified; MMSE: Mini-Mental State Examination; RUDAS: Rowland Universal Dementia Assessment Scale; TMSE: Thai Mini-Mental State Examination

Figure 1.2: Forest plot



Abbreviations:
ACE-R: Addenbrooke's Cognitive Examination-Revised; CAMCOG: Cambridge Cognitive Examination; CAMSE: Chinese adapted Mini-Mental State Examination; CDT: Clock Drawing Test; CMMS: Chinese Mini-Mental Status; K-MMSE: Korean Mini-Mental State Examination; M-MMSE: Modified Mini-Mental State Examination; mCMMSE: Modified Chinese Mini-Mental State Examination; MMSE-37: 37-point version of Mini-Mental State Examination; MMSE-ad: Mini-Mental State Examination adapted; MMSE-mo: Mini-Mental State Examination modified; MMSE: Mini-Mental State Examination; RUDAS: Rowland Universal Dementia Assessment Scale; TMSE: Thai Mini-Mental State Examination

Figure 1.3: Funnel plot for all studies included in meta-analysis



1.4.5.3 Subgroup analyses

A sensitivity analysis showed no significant effect of study objectives on the difference in performance between literate and illiterate participants (p = 0.885). Literate participants scored significantly higher than illiterate participants regardless of whether the studies primarily set out to compare these groups or not (Table 1.4).

Table 1.4: Random effect models sub-grouped according to how studies examined differences between literate and illiterate participants

Subgroup	*n*	*k*	Hedges' g, [95% CI], *p*	*Q* test, *p*	I^2
Primary research question	12	15	-1.43, [-1.87, -0.98], $p < 0.001$	127.63, $p < 0.001$	96.9%
Secondary research question	9	14	-1.09, [-1.58, -0.59], $p < 0.001$	324.62, $p < 0.001$	96.75%
Research question not explicitly asked	6	8	-0.97, [-1.41, -0.54], $p < 0.01$	113.37, $p < 0.001$	95.04%

n = number of studies, *k* = number of effect sizes

A moderator analysis showed a significant effect of test type on the difference in performance between literate and illiterate participants ($p < 0.01$). Where screening tests were designed or modified for illiterate individuals or individuals with low

education, the difference in performance between the two groups was smaller. However, literate participants still obtained significantly higher scores than illiterate participants in adapted screening tests (Table 1.5).

Table 1.5: Random effect models sub-grouped according to test type

Test design	*n*	*k*	Hedges' g, [95% CI], *p*	*Q* test, *p*	I^2
Designed for general use	24	30	-1.29, [-1.56, -1.03], $p < 0.001$	482.59, $p < 0.001$	97.81%
Modified/designed for use in illiterate/low education populations	7	7	-0.81, [-1.32, -0.29], $p < 0.01$	76.99, $p < 0.001$	94.89%

n = number of studies, *k* = number of effect sizes

In order to examine the effect of cognitive impairment, a further analysis was carried out using only the 10 studies that included both participants with and without cognitive impairment or dementia. Similarly, in this analysis, a significant overall effect was found with literate participants scoring higher than illiterate participants (g = -1.58, *95% CI* = [-2.1, -1.07], $p < 0.001$). Again, significant heterogeneity was found (Q = 293.57, $p < 0.001$, I^2 = 92.9%). A moderator analysis showed a significant effect of cognitive impairment on the difference in performance between literate and illiterate participants ($p < 0.001$). The difference in performance between groups was greater in healthy participants than in participants with cognitive impairment and dementia. However, there was still a significant difference between literate and illiterate groups in participants with cognitive impairment/dementia (Table 1.6).

Table 1.6: Random effect models sub-grouped according to cognitive status

Cognitive status	*n*	*k*	Hedges' g, [95% CI], *p*	*Q* test, *p*	I^2
Healthy	10	13	-1.57, [-2.19, -0.95], p<0.001	215.16, $p < 0.001$	95.34%
Mild cognitive impairment	4	7	-0.87, [-1.69, -0.05], p<0.05	34.534, $p < 0.001$	90.81%
Dementia	7	7	-0.9, [-1.44, -0.37], p<0.01	26.42, p<0.001	76.38%

n = number of studies, *k* = number of effect sizes

1.5 Discussion

1.5.1 Main findings

The results of this systematic review and meta-analysis indicated that illiterate groups scored significantly lower than literate groups in dementia screening tools. The analyses demonstrated that there was less disparity between literate and illiterate participants in tests that are designed or adapted for use with individuals who are illiterate or have low education levels, including modified versions of the MMSE as well as the RUDAS (Goudsmit et al., 2020; Nielsen, 2018) and LICA (Shim et al., 2015). However, in many of these tests, literate participants continued to outperform illiterate participants. The analysis also indicated that the difference between literate and illiterate participants in performance in dementia screening tools was greater when these participants did not have a cognitive impairment.

1.5.2 Interpretation and analysis

Our findings are in line with literature on the topic of illiteracy and cognitive assessment, which suggests that illiterate individuals are at a significant disadvantage when assessed using formal assessment methods (Ardila et al., 2010). Dementia screening tools assess many cognitive domains that rely on skills that are directly or indirectly related to literacy, such visuospatial function, logical reasoning, and fine motor skills (Kosmidis, 2018). It corresponds that individuals who never learned to read or write tend to perform poorer in these domains than those who did.

The most common dementia screen test studied in this review was the MMSE, with 33 of the 37 studies including either the original version or an adapted version of the MMSE. The persistence and predominance of the MMSE within research, despite widespread acknowledgement of its many limitations (Nieuwenhuis-Mark, 2010), represents a significant obstacle in the pursuit of appropriate methods for screening dementia. This meta-analysis adds further weight to the proposal that the MMSE is unsuitable for use in many populations and future studies should move away from relying on the MMSE as a screen for cognitive impairment.

The results indicate that, when tests are designed or adapted for use in illiterate populations or populations with low education, there is less disparity in performance between literate and illiterate groups. This analysis should be interpreted with a degree of caution, however, as the group of adapted screening tools consisted of a range of different tools. These tools are relatively new compared to the MMSE and require further assessment to determine their validity and utility across different population groups. One tool that stood out as potentially promising was the RUDAS, with both Goudsmit et al. (2020) and Nielsen (2018) demonstrating that literate and illiterate participants performed similarly in this tool. The RUDAS was developed for use in culturally and linguistically diverse populations. It has been validated in 16 countries, in at least 16 languages (Komalasari, Chang, & Traynor, 2019).

It should be noted that only two studies included in this review administered cognitive assessments in English, both of which were conducted in the USA (Black et al., 1999; Hamrick et al., 2013). There were no studies conducted in the UK. The dearth of studies on this topic in English-speaking, higher-income countries is likely related to the higher literacy rate of these countries (UIS, 2019). However, the demographic landscape of many countries, including the UK, is changing, and becoming increasingly diverse (Canevelli et al., 2019; Office for National Statistics, 2018). It is therefore important that even countries with high literacy rates have the resources to provide services that are culturally and educationally competent.

The results also demonstrated that, where individuals were cognitively impaired at the point of administration of the cognitive screen, there was less disparity between literate and illiterate groups. It is possible, that as cognition deteriorates, literate and illiterate groups may become more similar in terms of their cognitive functioning. It is plausible for example, that literate individuals with dementia may become more impaired in domains related to literacy (e.g., visuospatial function) as their cognition deteriorates (Kim & Chey, 2010). The purpose of screening tools, however, is to provide an initial indication of cognitive changes. It is therefore important that such tools are sensitive to subtle changes. Disparity between literate and illiterate healthy individuals is

therefore problematic, as screening tools are most valuable at the point where it is unclear whether an individual is healthy or is beginning to show some cognitive changes (Xu et al., 2003).

1.5.3 Limitations

There are several limitations to this systematic review and meta-analysis. The quality of the studies included in the review is mixed, with only seven of the included studies rated as “good”. The main methodological issues with the studies included lack of sample size justifications and unclear criteria for differentiating between literate and illiterate participants. We attempted to minimise quality issues by only including studies with a rating of “fair” or “good” in the meta-analysis. The quality assessment ratings may also be subject to individual bias. Steps were taken to minimize bias, such as the addition of a second rater.

There are a number of potential sources of heterogeneity in the meta-analysis, as reflected by high I^2 values. While heterogeneity is to be expected in a meta-analysis, it is important to explore potential sources of variance (Higgins, 2008).

Firstly, there was heterogeneity across the study objectives and designs. Whereas some studies were designed specifically to answer the question of whether literate and illiterate groups differed in terms of performance in a screening tool, this was not the sole focus of every study. A sensitivity analysis was carried out to explore this potential source of heterogeneity. This analysis indicated that the results were not affected by the discrepancies across the studies in terms of their primary objectives, and high I^2 values remained when random effects models were carried out by subgroup.

There was also heterogeneity across study populations. Some studies included all healthy participants, whereas others included both healthy participants and participants with MCI and/or dementia. Participants with a wide range of cognitive abilities were therefore included in the main analysis of the meta-analysis, potentially limiting the generalisability of the findings. A moderator analysis was carried out to explore this potential limitation further and indicated that literate and illiterate participants still differed significantly when healthy participants and cognitively impaired participants were analysed separately.

Finally, there was heterogeneity across the screening tools. For the purpose of this systematic review and meta-analysis, all screening tools were grouped together. Although the MMSE was the most common tool examined across the studies, there existed significant variation in the languages and versions of the MMSE used. The analyses therefore included a variety of different tools administered across a range of different countries and languages. Combining effect sizes for individual studies with different outcome measures may also limit the findings.

1.5.4 Implications and future directions

The results of this systematic review and meta-analysis indicate that many of the tools used for screening dementia are unsuitable for use in individuals who are illiterate. These findings have significant clinical implications, as they suggest that many of the

widely used cognitive screening tools are not fit for purpose for many individuals. Many countries across the world are becoming increasingly multi-cultural and as a result, clinicians in higher income countries, such as the UK, are encountering more individuals from lower income countries with high illiteracy rates (Nielsen et al., 2011). Health services have a duty to provide culturally competent and person-centred care. It is therefore imperative that clinicians are aware of the considerations that should be given when assessing dementia in illiterate individuals. Definitive guidelines around assessing illiterate individuals cannot yet be recommended based on the current research. However, some general recommendations include selecting tools that were designed specifically for use in multicultural and/or illiterate populations and emphasising information about changes relative to past functioning and the reasons for their illiteracy. This information should be gathered from interview with individuals and, where possible, with informants who have known the individual in question for a significant length of time (Kosmidis, 2018; Nell, 2000).

This review also highlights the substantial heterogeneity in research on dementia screening tools, making it difficult to compare results across studies. This is widely recognised as a problem within the field of dementia research (Costa et al., 2017). Recent calls for consensus in the use of assessment tools for dementia highlight the importance of a harmonised approach (Costa et al., 2017; Logie, Parra, & Della Sala, 2015; Paulino Ramirez Diaz et al., 2005). One important aspect of harmonisation involves ensuring that tools selected and developed for widespread use are suitable for use across many different populations. Such tools should be cross-culturally valid and should not be affected by education or literacy level (Costa et al., 2017; Logie et al., 2015). Tools that minimise the effect of education, literacy, and culture have been developed (Choi et al., 2011; Hall et al., 2000; Nielsen et al., 2018; Storey, Rowland, Conforti, & Dickson, 2004). However, the literature review and data analysis in the present study indicates that more research is required to validate these tools and determine their suitability across a wide range of settings. Such research should focus on determining the sensitivity and specificity of the tools in terms of differentiating between healthy ageing, mild cognitive impairment and various types of dementia, the effect of translation, and the impact on confounding variables.

1.5.5 Conclusions

This systematic review and meta-analysis collated existing data and highlighted the unsuitability of many dementia screening tools for individuals who are illiterate. This finding emphasises the need for the development and use of tools that are suitable for all individuals, regardless of their literacy ability, education or cultural background. The development of screening tools that are unaffected by literacy level is complicated by the fact that many cognitive domains implicated in dementia are influenced by literacy skills. Furthermore, individuals who are illiterate are less likely to be familiar with test-taking procedures, which may impact their performance in formal cognitive tests. Despite these confounding factors, tools that minimise the effect of education, literacy, and culture have been developed. Although further research is still required in order to substantiate the suitability of these tools in some settings, clinicians assessing dementia in individuals with low levels of literacy should consider using such tools where appropriate and should place particular emphasis on information gathering to inform diagnostic decision-making.

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2 Predicting Cognitive Decline in patients with Mild Cognitive Impairment: An examination of the Visual Short-Term Memory Binding Task

Caragh Maher[a] & Clara Calia[a]

[a] *Clinical and Health Psychology, School of Health in Social Science, University of Edinburgh, Edinburgh, EH8 9AG, UK*

Corresponding author: Caragh Maher

Manuscript prepared for submission to Archives of Clinical Neuropsychology. Journal guidelines are included in Appendix D

Total word count excluding references: 10,071

Word count excluding abstract, reference list, tables and figures: 8,598

2.1 Abstract

Objective: Memory binding is impaired in the early stages of Alzheimer's Disease (AD). The first objective of this study was to investigate whether the Visual Short-Term Memory Binding Task (VSTMBT) can predict future cognitive decline and conversion from Mild Cognitive Impairment (MCI) to AD. The second objective of the study was to assess the construct validity of the VSTMBT.

Method: The VSTMBT was administered to 72 healthy individuals and 82 individuals with MCI, along with a battery of traditional neuropsychological assessments. Participants were reassessed at yearly intervals for two years. Linear mixed models and logistic regression models were used to assess the extent to which the VSTMBT and other neuropsychological measures can predict cognitive decline and conversion to AD. In order to examine the construct validity of the VSTMBT, partial correlations between VSTMBT scores and scores from traditional neuropsychological measures were examined. Multiple imputation methods were used to account for missing data.

Results: In contrast to traditional measures, the VSTMBT did not significantly predict cognitive decline or conversion from MCI to AD. Partial correlation analyses showed that the VSTMBT did not significantly correlate with other measures of memory and failed to discriminate between measures of executive function, processing speed and visuospatial ability.

Conclusions: The results suggest that the VSTMBT does not predict cognitive decline at the MCI stage of AD. The findings support the idea that the VSTMBT is most informative at preclinical stages of AD, whereas traditional measures may be more useful at the onset of the clinical syndrome.

Key words: Mild Cognitive Impairment; Alzheimer's disease; Short Term Memory; Neuropsychological Assessment; Longitudinal Studies; Test Validity

2.2 Introduction

2.2.1 Working memory and the binding problem

In cognitive psychology, working memory refers to the ability to temporarily store and manipulate information in the mind (Baddeley, 2000). Baddeley and Hitch first introduced the three-component model of working memory in 1974 (Baddeley & Hitch, 1974). This model proposed that working memory consists of an attentional control system, the 'central executive', which is supported by two additional systems, the 'phonological loop', which holds speech-based information, and the 'visuospatial sketchpad', which holds visuospatial information (Baddeley, 2000; Baddeley & Hitch, 1974).

In 2000, a fourth system called the 'episodic buffer' was added to the model to account for the binding problem (Baddeley, 2000). The binding problem concerns the question of how information from a range of sensory modalities is bound together so that the world is perceived as a coherent array of objects. The episodic buffer was proposed as an additional system which draws on information from the phonological loop, the visuospatial sketchpad, and long-term memory, and holds it together in an integrated form. The episodic buffer is therefore conceptualised as the locus of memory binding (Baddeley, 2000; Jonin et al., 2019).

2.2.2 Relational and conjunctive binding

Relational binding refers to memory for associations between distinct memory items (e.g., names and faces; Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012). The hippocampus appears to play a key role in this function, both in short-term and long-term memory (Mayes et al., 2004; Parra et al., 2013).

Conjunctive binding, contrarily, refers to the integration of features within a unified object (e.g., colour and shape; Della Sala et al., 2012). The neuroanatomical correlates of this function are less well understood than those of relational binding (Parra et al., 2013). Case studies of patients with damaged hippocampi have indicated that the hippocampus may not be necessary for conjunctive binding in short-term (Jonin et al., 2019; Parra et al., 2013) or long-term memory (Mayes et al., 2004). In each of these case studies, patients with hippocampal damage showed deficits in relational binding tasks, but not in conjunctive binding tasks.

2.2.3 Memory binding and dementia

The distinction between these two types of memory binding functions and their neuroanatomical correlates has important implications for clinical assessment of memory, particularly in the context of Alzheimer's disease (AD). Relational and conjunctive binding are both affected in AD (Della Sala, Kozlova, Stamate, & Parra, 2018; Della Sala et al., 2012; Parra et al., 2009). However, conjunctive binding in short-term memory is the only function that appears to be specifically impaired in AD (Della Sala et al., 2012; Kozlova, Parra, Titova, Gantman, & Sala, 2020).

2.2.4 Assessment of memory binding

Some of the most commonly used tests for assessing memory decline in AD involve relational binding (e.g., associative learning tasks), list learning, and delayed recall (Della Sala et al., 2018). While these tools do detect memory decline in individuals with AD, their use is confounded by the finding that performance in these tools is also affected by non-AD dementias, including vascular dementia (Clague, Dudas, Thompson, Graham, & Hodges, 2005) and frontotemporal dementia (Dimitrov et al., 1999). Furthermore, performance in relational binding tasks is affected by normal ageing (Old & Naveh-Benjamin, 2008) and chronic depression (Levin, Heller, Mohanty, Herrington, & Miller, 2007). The Free and Cue Selective Reminding Test (FCSRT) is an example of a gold standard relational binding task used in the assessment of AD (Auriacombe et al., 2010; Buschke, 1984; Dubois et al., 2007; Grober, Sanders, Hall, & Lipton, 2010; Lemos, Simoes, Santiago, & Santana, 2015). Despite its high sensitivity and specificity for AD (Derby et al., 2013), performance in this task is affected by normal ageing and education levels (Campo, 2004; Grober et al., 2008; Pena-Casanova et al., 2009). Population norms are therefore needed when using the FCSRT to differentiate between normal ageing and AD (Campo, 2004; Killin, Abrahams, Parra, & Della Sala, 2018; Pena-Casanova et al., 2009).

The Visual Short-Term Memory Binding Task (VSTMBT; Parra et al., 2010) was developed to assess conjunctive binding in short-term memory. The task measures the ability to retain single features such as shapes, and for conjunctions such as shape-colour bindings. In individuals with intact conjunctive binding, there is no additional burden on working memory load to remember a single feature (e.g., a square) compared to a bound combination of features (e.g., a red square; Brockmole, Parra, Sala, & Logie, 2008; Luck & Vogel, 1997).

Conjunctive binding, unlike relational binding, is preserved in healthy ageing (Brockmole et al., 2008). However, conjunctive binding is impaired in individuals with AD. Individuals with AD display a specific deficit in the ability to remember bound objects compared to objects with single features. An impairment in the ability to retain bound objects in working memory can have a significant impact on daily living; for example, an individual with AD may struggle to keep track of whether they have just taken the white or yellow pill (Della Sala et al., 2012; Parra et al., 2009; Parra et al., 2010).

This deficit appears to be exclusive to AD, as conjunctive binding has been shown to be preserved in patients with frontotemporal dementia, vascular dementia, Lewy body dementia and dementia associated with Parkinson's disease (Della Sala et al., 2012). Furthermore, impairments in conjunctive binding are seen in preclinical stages of AD. Parra et al. (2010) demonstrated that impairments in conjunctive binding can be detected in individuals who carry a gene mutation responsible for familial AD (Lopera et al., 1997), using the VSTMBT. These individuals did not show any symptoms of AD when assessed with a neuropsychological battery, including measures of relational binding, indicating that conjunctive binding deficits may be among the first indicators of the disease (Parra et al., 2010).

A number of studies have also demonstrated that individuals with subjective cognitive decline and Mild Cognitive Impairment (MCI) show impairments in the VSTMBT

relative to controls (Koppara et al., 2015; Parra et al., 2019). Furthermore, the VSTMBT has proved more sensitive and specific than the FCSRT, one of the most widely used tests for detecting AD (Della Sala et al., 2018). Given the specificity and early onset of conjunctive binding deficits in AD, the VSTMBT represents a promising tool for the assessment of AD.

2.2.5 Memory binding assessment: a transcultural tool?

Impairment in conjunctive binding, as measured by the VSTMBT, has been proposed as a transcultural cognitive marker of AD (Della Sala et al., 2018). The diagnosis of dementia currently relies on methods of assessment that are affected by education, culture, and language of administration. This presents significant challenges for diagnosing dementia in in minority populations and in low/middle income countries. The use of biased assessment tools can potentially result in the misdiagnoses of dementia (Ardila, 2005; Nielsen et al., 2018). There are many costs associated with a misdiagnosis of dementia. Primarily, a misdiagnosis may result in the infliction of avoidable emotional stress upon patients and their families. Additionally, it may lead to unnecessary treatment and environmental adjustments, and an increased burden on the health service (Pedraza & Mungas, 2008).

Studies have demonstrated that VSTMBT is unaffected by education (Yassuda et al., 2020) or culture (Della Sala et al., 2018; Parra et al., 2011). The VSMBT has been validated in populations with various levels of education (Yassuda et al., 2020), and from various countries, including the UK (Parra et al., 2011, Experiment 1), Colombia (Parra et al., 2011, Experiment 2), and Romania (Della Sala et al., 2018).

Recent consensus papers and guidelines (e.g., Costa et al., 2017; Maruta, Guerreiro, de Mendonca, Hort, & Scheltens, 2011) have highlighted the importance of developing tests that can detect the early changes of dementia, are cross-culturally valid, have high predictive value, and have well-established construct validity. Whilst the VSTMBT has been shown to detect subtle changes in the early stages of AD, and has demonstrated cross-cultural validity, the predictive value of the tool and its construct validity have yet to be examined.

2.2.6 The present study: rationale and aims

Understanding the expected pattern of disease progression over time is helpful for patients and families to organise the way they live and prepare for future challenges (Smith & Lunde, 2013). Learning about the pattern and course of AD early in the disease promotes decision-making, as it gives the patient the opportunity to make decisions about current and future options while they still have capacity to provide informed consent. This may relate to financial affairs, legal matters, and care decisions (Rolland, 2017).

Cognitive decline is commonly assessed using measures of global cognition, such as the Addenbrooke's Cognitive Examination-Revised (ACE-R). The ACE-R provides an overall score by briefly assessing different cognitive domains (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006). Many studies have investigated the factors that predict the rate of cognitive decline in MCI and AD, and have shown that the presence of diabetes (Musicco et al., 2009), psychiatric conditions (Palmer et al., 2011), and

poor performance in tests assessing language (Boller et al., 1991; Mortimer, Ebbitt, Jun, & Finch, 1992) and episodic memory (Landau et al., 2010) predict steeper cognitive decline. A number of neuropsychological assessments have also been shown to predict conversion from subjective memory complaints or MCI to AD, including the FCSRT, (Derby et al., 2013), the Hopkins Verbal Learning Test (HVLT; Tian, Bucks, Haworth, & Wilcock, 2003), and the Clock Drawing Test (Amodeo, Mainland, Herrmann, & Shulman, 2015). However, it is currently unclear whether measures of conjunctive binding, such as the VSTMBT, predict the course of cognitive decline in healthy individuals and individuals with MCI. The current longitudinal study therefore aimed to examine the predictive value of the VSTMBT in comparison to current gold standard neuropsychological tests. This aim was addressed by asking the following two research questions:

1. To what extent do the VSTMBT, the FCSRT, the HVLT, and the CDT predict change in ACE-R performance over time in healthy individuals and individuals with MCI?
2. To what extent do the VSTMBT, the FCSRT, the HVLT, and the CDT predict AD in individuals with MCI?

Given that the VSTMBT was designed as a specific test of conjunctive memory binding, it is important to explore its relation to other, more traditional tools. Therefore, the second aim of the study was to examine the construct validity of the VSTMBT. This aim was addressed by asking a third research question:

3. To what extent do VSTMBT scores in healthy individuals correlate with and diverge from scores a range of traditional neuropsychological measures?

2.3 Methods

2.3.1 Overview of study and use of data

The current study utilised secondary data obtained from a large-scale project carried out in Scotland between October 2012 and November 2017 entitled 'Longitudinal Assessment of Short-term Memory Binding Functions in patients with Mild Cognitive Impairment' (see Appendix E for the protocol of this study). The aim of this study was to investigate whether individuals with MCI show memory binding deficits and the extent to which this impairment predicts conversion to AD. The data collected for this study had not yet been fully analysed and, as such, the present author sought to analyse the data further in order to meet these research aims.

2.3.2 Participants

Data were acquired from 82 patients with a diagnosis of MCI (47% female) and 72 healthy control participants (60% female). The average age was 75.4 (*SD* = 7.85) for the patient group and 74.9 (*SD* = 6.01) for the control group. All participants were residents in Scotland at the time of data collection. Control participants were recruited from the Psychology Volunteer Panel at the University of Edinburgh using a convenience sampling method. Patients were recruited from clinics in the National Health Service (NHS) in Lothian and Forth Valley using a purposive sampling method. Data were collected over a 5-year period between 2012 and 2017 and consisted of a baseline assessment followed by yearly follow-up assessments.

2.3.3 Eligibility criteria

Participants were required to be over 65 years of age and English-speaking to participate in the study. Control participants were required to be cognitively healthy. Participants in the patient group were required to have a diagnosis of MCI. Diagnoses were made by clinicians within the NHS according to the gold standard criteria set by Petersen (2004) and Winblad et al. (2004). The criteria were as follows:

1. Change in cognition recognised by the affected individual and/or a close informant
2. Mini Mental State Examination (MMSE) ≥ 24 and/or ACE-R >= 80
3. Objective memory impairment as assessed by:
    a. Memory domain of ACE ≤ 19 **(**60-69 years), ≤ 17 **(**≥70 years; Mioshi et al. 2006)
    b. HVLT delayed recall ≤ 4 (Lonie et al., 2010)
4. Independence in functional activities
5. Absence of dementia

Participants were excluded from the study or a time point of the study if they presented with hearing or vision problems that impeded their ability to participate in the neuropsychological test battery, or if they showed signs of delirium or infection.

2.3.4 Procedure

At each time point, a battery of neuropsychological tests was administered to participants. The battery consisted of a combination of traditional neuropsychological tests commonly used to assess dementia (Maruta et al., 2011; Shulman et al., 2006) and more novel tasks, including the VSTMBT. The order of the assessments was the same for each participant. Where different versions of an assessment were available, the version was changed at each time point. Assessments were administered on the same day, over a two-hour period. However, participants who became fatigued were offered two separate sessions to complete the battery. An overview of the neuropsychological tests included in the current study is provided in section 2.3.4.

Diagnoses were updated in October 2016 and in November 2018 by accessing the patients' medical files.

Data collection was approved by the University of Edinburgh Psychology Research Ethics Committee under the following reference number: 06/MRE07/40. For the purpose of the current study, the dataset was shared with the author, after the study protocol was approved by the University of Edinburgh School of Health in Social Science Research Ethics Committee under the following reference number: CLIN782 (Appendix F).

2.3.5 Materials

2.3.5.1 Visual Short-Term Memory Binding Task (VSTMBT)

The VSTMBT assesses conjunctive binding in visual short-term memory. In the present study, the task involved presenting arrays of stimuli on a computer screen. The stimuli included shapes (six-sided random polygons) shaded black and coloured shapes. There were 2 conditions: assessment of short-term memory of *single features* (shape only) and assessment of short-term memory of *conjunctive binding* (shape-colour binding). Each condition consisted of 15 practice trials followed by 32 test trials. Trials were randomized across participants and the order of the conditions was counterbalanced.

At the beginning of the task, a fixation screen was shown for 500 milliseconds (ms). The study display presented an array of stimuli (either single feature stimuli or bound shape-colour stimuli), as demonstrated in Figure 2.1. Participants were asked to remember the stimuli. The study display was followed by an unfilled retention interval of 900ms, and participants were then presented with a test display. In half of the trials, the test display included stimuli that were the same as presented in the study display, and in half of the trials, different stimuli were presented. Participants were asked to identify whether the stimuli presented in the test display were the same or different to those presented in the study display.

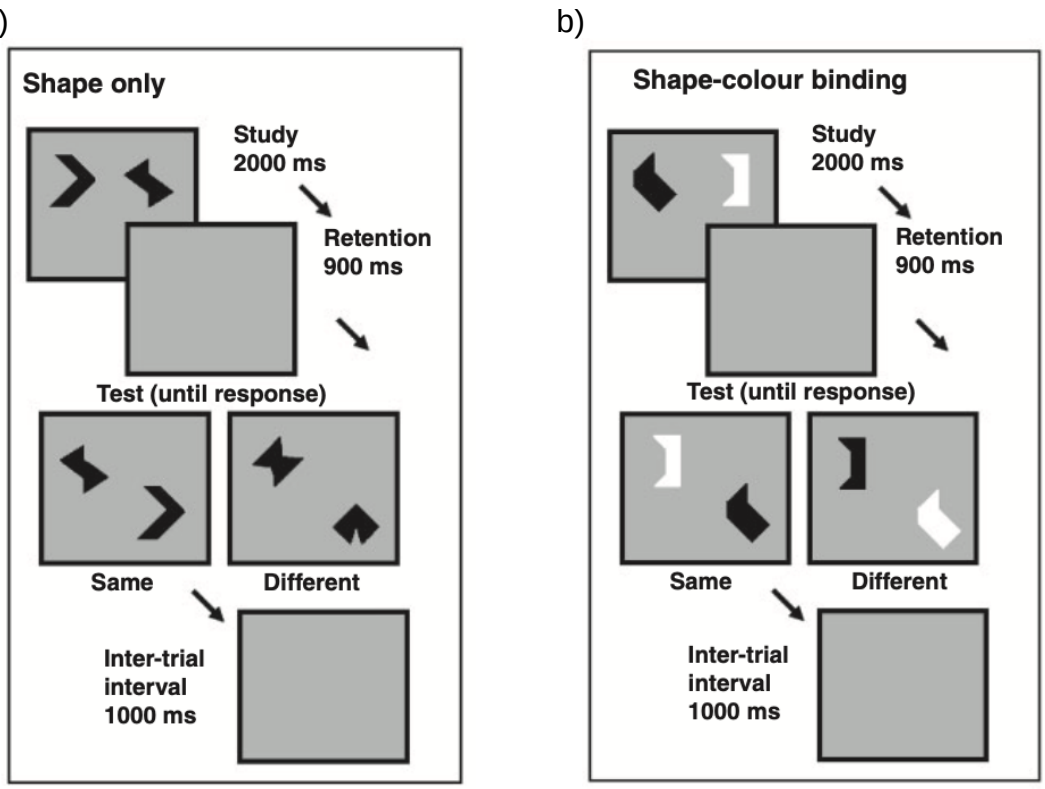

Figure 2.1: Visual Short Term Memory Binding Task (VSTMBT) protocol. Test for (a) memory of shapes only and (b) memory of shapes and colours. *Image copyright Parra et al. (2010), used with permission.*

The VSTMBT has been reported to have a high validity; in a study by Della Sala et al. (2018), the task had a sensitivity of 1.0 and a specificity of 1.0, correctly classifying 33 control participants and 33 participants with AD.

2.3.5.2 Free and Cued Selective Reminding Test (FCSRT)

The FCSRT is a multi-trial verbal learning test. A visual array of 4 written words was presented and participants were asked to point to and name each word in response to a semantic category label (e.g., for the word 'desk', the category label was 'furniture'). Immediately after all 4 words were identified, a cued recall task was administered, whereby participants were asked to recall the words in response to their category labels. This procedure was repeated 4 times, with 16 words presented in total.

This learning phase was followed by a 20-second verbal interference task. Participants were then administered a free recall task, whereby they were asked to remember as many words as they could. Cues (i.e., category labels) were presented for the words that they did not freely recall. Words not remembered by cued recall were then presented. This is the selective reminding aspect of the task. This procedure was repeated three times, with a 20-second verbal interference task between each trial.

The free recall score is the cumulative sum of the number of words freely recalled from all three trials, with a maximum score of 48. The total recall score is the sum of freely

recalled words and words recalled with a cue, again with a maximum score of 48 (Buschke, 1984; Grober et al., 2010; Jonin et al., 2019).

The validity of the FCSRT has been well-supported. The assessment has shown a sensitivity between 0.80 and 0.87 and a specificity between 0.70 and 0.80 for predicting AD (Derby et al., 2013).

2.3.5.3 Addenbrooke's Cognitive Examination Revised (ACE-R)

The ACE-R is a brief screening assessment that provides evaluation of attention/orientation, memory, fluency, language, and visuospatial ability. It was developed to provide a brief assessment of early-stage dementia (Mioshi et al., 2006). The assessment has been validated in many countries, with sensitivity ranging between 0.84 and 1.0, and specificity ranging between 0.89 and 1.0 (Alexopoulos et al., 2010; Mioshi et al., 2006; Raimondi et al., 2012; Yoshida et al., 2012).

Memory domain

The memory domain of the ACE-R comprises of 3 tasks. Participants were asked to recall words previously repeated, to memorise and recall a fictional name and address, and to recall well-known historical facts (Bruno & Schurmann Vignaga, 2019). The memory domain has been shown to have a sensitivity of 0.96 and a specificity 0.90 for amnestic MCI (Matias-Guiu et al., 2017).

2.3.5.4 Hopkin's Verbal Learning Test (HVLT)

The HVLT assesses verbal learning and memory. In this task, a list of 12 words, comprised of three semantic categories with four words per category, was read to participants three times. After each trial, the number of words freely recalled by the participants was recorded. After a delay of 25 minutes, participants were asked to recall as many words as they could from list. The number of words correctly recalled in this trial makes up the delayed recall score. The total recall score comprises of the number of words correctly recalled across all four trials. After the fourth trial, the participants were read a list of 24 words and were asked after each word whether or not it appeared on the first list. The total number of words correctly recognised makes up the HVLT recognition score (Benedict, Schretlen, Groninger, & Brandt, 1998; Brandt, 1991). Validity of the HVLT has been demonstrated, with the total recall score of the HVLT demonstrating 0.91 sensitivity and 0.98 specificity for AD (Hogervorst et al., 2002).

2.3.5.5 Clock Drawing Test (CDT)

The CDT is a rapidly administered tool that comprised of asking participants to draw a clock to indicate a particular time. The test measures a range of functions including planning, abstract thinking, and visuospatial abilities (Shulman, 2000). The test shows a specificity of 0.85 and sensitivity of 0.85 (Shulman, 2000), and has been demonstrated to predict conversion from MCI to dementia (Amodeo et al., 2015).

2.3.5.6 Rey Complex Figure Test

The Rey Complex Figure Test is a test of visuospatial ability and visual memory. In this task, participants were asked to copy a complicated line drawing, free hand. After a delay of 30 minutes, participants were asked to draw the figure from memory (Osterrieth, 1944; Rey, 1941). Individuals with AD tend to score significantly lower in the Rey Complex Figure Test compared to healthy age-matched controls (Berry, Allen, & Schmitt, 1991).

2.3.5.7 Trail Making Test

The Trail Making Test is a test of visual attention and task switching that comprises of two parts: part A and part B. In part A, participants were instructed to connect a series of 25 numbers in numerical order, in the quickest time possible. In part B, participants were instructed to connect 25 numbers and letters in numerical and alphabetical order, switching between numbers and letters, again in the quickest time possible. Participants were scored by the time taken to complete each trail, measured in seconds. Superior performance is therefore represented by a lower score, indicating a faster response time (Bowie & Harvey, 2006). At optimum cut-off points, the specificity of the test ranges between 0.78 and 0.83, and the sensitivity ranges between 0.79 and 0.87 for AD (Rasmusson, Zonderman, Kawas, & Resnick, 2010).

2.3.5.8 Letter Fluency

The letter fluency task assesses phonemic fluency. In this task, participants were asked to recite as many words as possible that begin with a single letter in one minute. The letters used in the current study were F, A, and S (Spreen & Benton, 1977). Phonemic fluency relies on executive control of selective attention, set-shifting, and self-monitoring (Patterson, 2011). The test has shown a sensitivity of 0.89 and a specificity of 0.85 for AD (Monsch et al., 1992).

2.3.5.9 Digit Symbol

The digit symbol task is a test of attention, planning, and set switching (Jaeger, 2018). Participants were presented with a legend with pairs of digits and symbols and a series of digits with an empty box below each. They were instructed to write the symbols that match the digits in the empty boxes. Participants were scored by the number of correct symbols written within a 90 second time frame (Fleischmann et al., 1991; Jaeger, 2018). Individuals with AD have been shown to score significantly lower in the digit symbol task compared to healthy age-matched controls (Fleischmann et al., 1991).

2.3.6 Dataset organisation

For the purpose of the present study, data collected at baseline and at two follow-up time points were included in the study. Although some participants attended more than two follow-up assessments, there were insufficient data at time point 3 and 4 to warrant inclusion in the analyses.

Baseline diagnosis was a dichotomous variable, with participants classified as a control or as having MCI. Six participants were identified as having a diagnosis of

amnestic MCI, which is a form of MCI that primarily affects memory and is highly associated with conversion to AD (Fischer et al., 2007). Due to the small number of participants with this label, participants with amnestic MCI were included in the wider MCI group.

The end of study diagnosis was also a dichotomous variable, with participants classified as AD cases or non-AD cases. For the purpose of the present study, the 2016 and 2018 diagnosis updates were merged to provide an end of study diagnosis of AD or no AD. Participants were classified as having an end of study diagnosis of AD in the following conditions:

a) 2016 status update confirmed AD
b) 2016 status update confirmed AD and 2018 confirmed death
c) 2016 status update confirmed MCI and 2018 confirmed AD
d) 2016 status update showed no record and 2018 confirmed AD

Clinical notes providing supplementary information were considered on a case-by-case basis. Four patients were described as having a diagnosis of mixed vascular dementia and AD. These participants were coded as AD cases, given the recognition that differentiation between AD and vascular impairment is often unclear (Schneider, Arvanitakis, Bang, & Bennett, 2007). For two participants, the status update indicated either 'no record' or 'no change', but accompanying clinical notes suggested early AD. These participants were also coded as AD cases. One participant was described as having 'unspecified dementia', with clinical notes indicating probable AD. This participant was also coded as an AD case. The status updates indicated that one participant developed frontotemporal dementia and another developed Lewy body dementia. These two participants were coded as non-AD cases.

2.3.7 Statistical analyses

2.3.7.1 Accounting for missing data

Multiple imputation was used to impute missing data, according to the Fully Conditional Specification method described by Enders, Keller, and Levy (2018). Imputation models were constructed using Blimp software (Enders, Du, & Keller, 2020; Enders et al., 2018; Keller & Enders, 2019). The multilevel nature of the data was taken into account in the imputation model and 10 imputed datasets were generated. The Markov Chain Monte Carlo with the Gibbs sampler algorithm approach was used, with a burn-in period of 2,000 iterations followed by 4 chains of 2,500 iterations (10,000 iterations in total). Analyses were pooled using Rubin's rules (Rubin, 1987) with R packages 'lme4' (Bates, Mächler, Bolker, & Walker, 2015), 'mitml' (Grund, Robitzsch, & Luedtke, 2019) and 'miceadds' (Robitzsch & Grund, 2020).

2.3.7.2 Summary statistics

Demographic data and average test scores were compared between patients and controls using t-tests or chi-square tests.

2.3.7.3 Predicting decline in ACE-R performance

Linear mixed models were used to analyse the extent to which the VSTMBT, the FCSRT, the HVLT, and the CDT predict the rate of cognitive decline. Linear mixed models are suitable for analysing longitudinal data, as they take into account the fact that data collected from the same individual over time are likely to be correlated (Twisk, 2006a). The model was adjusted for age, education, and baseline diagnosis. Relevant model assumptions were tested to ensure the use of linear mixed models was justified.

2.3.7.4 Predicting conversion to AD

A logistic regression model was applied to assess whether the VSTMBT, the FCSRT, the HVLT, and the CDT predict incident AD. For this model, the dataset was subdivided to include only data from patients with a baseline diagnosis of MCI (n = 82) and control participants who went on to develop AD (n = 3). The model was adjusted for age and education. Relevant model assumptions were tested to ensure the use of a logistic regression model was justified.

2.3.7.5 Examining the construct validity of the VSTMBT

In order to assess the convergent and discriminant validity of the VSTMBT, partial correlations between VSTMBT scores and scores from the FCSRT, HVLT, CDT, ACE memory domain, Rey Figure recall, Trail Making Test, Letter Fluency task, and Digit Symbol task were examined. Age and education were included as covariates. A multitrait-multimethod matrix (MTMM) was created to tabulate the correlations between the tests. The MTMM is a method for examining construct validity, and involves the tabulation of correlations between tests organised by convergent and discriminant validity evidence (Campbell & Fiske, 1959). Convergent validity is assessed by examining whether tests that were designed to measure the same construct are correlated. Discriminant validity is assessed by examining whether tests that were designed to measure different constructs are not highly correlated. In the MTMM, monomethod-monotrait correlations refer to the correlation of a test with itself, thus equalling 1.0. Monotrait-heteromethod correlations refer to correlations between two different tests thought to assess the same construct and provide evidence of construct validity. Heterotrait-heteromethod correlations refer to correlation between two different tests thought to assess different constructs and provide evidence of discriminant validity (Campbell & Fiske, 1959; Thoma et al., 2018).

For the present study, subtests of the VSTMBT and the other traditional neuropsychological tests were grouped into distinct categories based on the construct they were designed primarily to assess. The categories included Visual Memory, Verbal Memory, Executive Function, Processing Speed, and Visuospatial Ability.

2.3.7.6 A priori power considerations

Prior to the implementation of the statistical analyses, consideration was given to whether the chosen analyses would be adequately powered, given a sample size of 154 (82 patients and 72 controls).

Given that linear mixed models have multiple levels and include both random and fixed effects, calculating the number of participants required for an analysis to be adequately powered is complex. Statisticians warn against using any rules of thumb or relying on

specific formulas to calculate a prior power and sample size estimations (Field, 2009; Kreft & De Leeuw, 1998; Twisk, 2006b). Simulation-based approaches are often used to calculate appropriate sample sizes. However, in order to run a simulation, certain parameters should be estimated (including variance of random slopes and within-subject variance). Some large-scale studies use pilot data in order to estimate these parameters (Ard & Edland, 2011; Brysbaert & Stevens, 2018). However, even with the use of estimates, the utility of sample size calculations in multilevel data has been questioned and Twisk (2006b) recommends taking great caution when making such calculations.

In light of the reliance on estimated parameters, an a priori power analysis was not thought to be appropriate for the linear mixed model analysis. Previous studies using linear mixed models to analyse longitudinal data of dementia patients have had sample sizes ranging between 100 and 150 participants (e.g., Ramanan et al., 2017; Rasmusson, Carson, Brookmeyer, Kawas, & Brandt, 1996). It was therefore estimated that an analysis with a sample size of 154 participants would be sufficiently powered.

For sample size calculations in logistic regression models, the number of events (i.e. diagnoses of MCI/AD) is the key quantity, rather than the number of individuals. Vittinghoff and McCulloch (2007) suggest that 5-9 events per variable in the model is sufficient. In order to run a model with 6 variables (age, education, baseline VSTMBT, FCSRT, HVLT, and CDT), therefore, there should be at least 30 events. Therefore, at least 30 individuals should convert from MCI to AD for the analysis to be adequately powered. The data revealed that 36 participants converted from MCI to AD over the course of the study, indicating that a logistic regression model would be suitable.

For the partial correlations with two covariates, an a priori power analysis was conducted using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007). In order to detect a partial r^2 of 0.1, with 80% power at the 5% significance level, a sample size of 73 participants is required. In total, 72 control participants were included in the study, indicating a sample size that almost provides adequate power to carry out partial correlation analyses. It was decided to carry out the analysis, with the caveat that the results would have a power estimate of just under 80%.

2.4 Results

2.4.1 Summary statistics

Over the course of the study from baseline to follow-up 2 (approximately 2 years), there was an overall dropout rate of 69% (n = 106), with 78% (n = 64) of patients and 58% (n = 42) of control participants dropping out of the study. In the patient group, 36 (44%) participants developed AD, 20 of whom participated in the first follow-up, and 5 of whom participated in the second follow-up. In the control group, 3 (4%) participants went on to develop AD, 2 of whom participated in the first follow-up, and 1 of whom participated in the second follow-up (Figure 2.2).

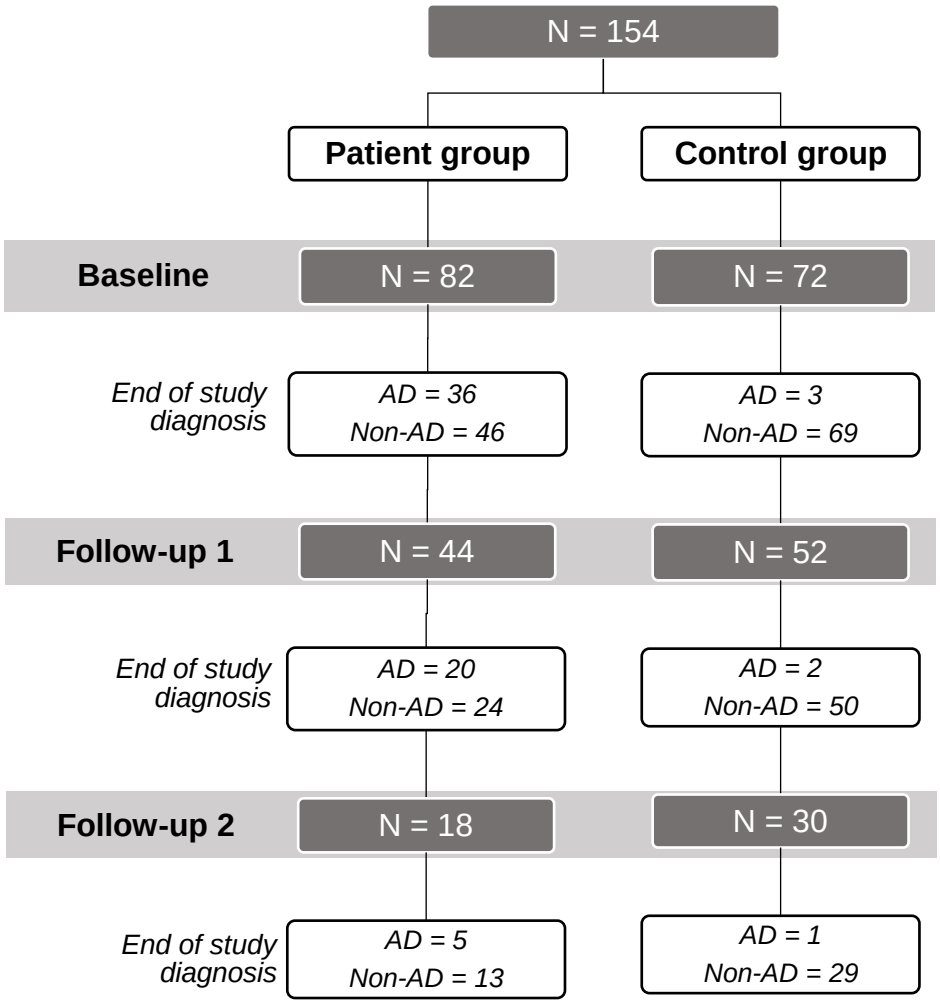

Figure 2.2: Flowchart of participants at baseline, follow-up 1, and follow-up 2

Summary statistics for the observed and imputed data are outlined in Table 2.1. There were no significant differences between observed and imputed variables. Patients and controls did not differ by age or gender. Patients had significantly fewer years of education than controls ($p < 0.001$), and patients were significantly more likely to develop AD by the end of the study ($p < 0.001$).

Table 2.1: Summary statistics for observed and imputed data

Variable	Data points missing	Observed		*p*-value	Imputed		*p*-value
	N (%)	*M(SD) unless otherwise specified*			*M(SD) unless otherwise specified*		
		Patient group (n= 82)	**Control group (n=72)**		**Patient group (n=82)**	**Control group (n=72)**	
Age (years)	0 (0%)	75.4 (7.85)	74.9 (6.01)	0.666	NA	NA	NA
Education (years)	0 (0%)	13.0 (3.90)	15.7 (3.99)	<0.001***	NA	NA	NA
Gender (female)	0 (0%)	39 (47%)†	43 (60%)†	0.178	NA	NA	NA
End of study AD	0 (0%)	36 (44%)†	3 (4%)†	<0.001***	NA	NA	NA
Baseline measures							
ACE-R	0 (0%)	80.5 (9.47)	93.9 (6.46)	<0.001***	NA	NA	NA
VSTMBT shape	11 (7%)	0.809 (0.107)	0.886 (0.076)	<0.001***	0.801 (0.116)	0.886 (0.076)	<0.001***
VSTMBT binding	12 (8%)	0.635 (0.101)	0.748 (0.378)	0.017*	0.633 (0.149)	0.748 (0.374)	0.018*
FCSRT free recall	2 (1%)	14.2 (8.20)	25.3 (7.98)	<0.001***	14.0 (8.27)	25.3 (7.93)	<0.001***
FCSRT cued recall	2 (1%)	24.6 (7.41)	21.4 (6.57)	0.005**	24.6 (7.38)	21.4 (6.53)	0.004**
FCSRT total	2 (1%)	39.2 (10.40)	46.8 (4.80)	<0.001***	39.0 (10.41)	46.8 (4.77)	<0.001***
HVLT recognition	7 (5%)	8.1 (2.80)	10.6 (1.90)	<0.001***	8.1 (2.85)	10.6 (1.89)	<0.001***
HVLT delayed recall	2 (1%)	3.4 (3.79)	7.5 (3.51)	<0.001***	3.4 (3.84)	7.5 (3.49)	<0.001***
HVLT total	1 (1%)	15.7 (5.65)	24.7 (6.09)	<0.001***	15.8 (5.79)	24.6 (6.05)	<0.001***
CDT	4 (3%)	5 (1)‡	5 (0)‡	<0.001***	5 (1)‡	5 (0)‡	<0.001***
Rey Figure copy	2 (1%)	28.9 (8.88)	31.4 (8.36)	0.71	28.7 (8.97)	31.4 (8.35)	0.05
Rey Figure immediate recall	2 (1%)	10.0 (7.98)	17.2 (8.54)	<0.001***	9.9 (8.07)	17.2 (8.54)	<0.001***
Rey Figure delayed recall	8 (5%)	9.5 (8.45)	16.8 (8.53)	<0.001***	9.1 (8.74)	16.6 (8.69)	<0.001***
ACE memory index	0 (0%)	16.8 (4.96)	23.4 (3.56)	<0.001***	NA	NA	NA
Trail-making Test A	5 (3%)	68.2 (35.28)	48.1 (15.93)	<0.001***	68.7 (35.27)	47.9 (16.43)	<0.001***
Trail-making Test B	6 (4%)	175.1 (92.63)	100.3 (53.64)	<0.001***	180.9 (100.79)	100.2 (53.83)	<0.001***
Digit symbol	6 (4%)	39.0 (13.77)	58.1 (14.67)	<0.001***	38.5 (14.36)	58.0 (14.65)	<0.001***
Letter fluency	6 (4%)	33.9 (15.97)	49.8 (13.07)	<0.001***	33.6 (16.51)	49.8 (13.14)	<0.001***
Follow-up measures							
ACE-R Follow-up 1	59 (38%)	78.6 (11.80)	93.6 (7.79)	<0.001***	78.6 (11.56)	93.2 (8.21)	<0.001***
ACE-R Follow-up 2	106 (69%)	78.2 (9.40)	93.4 (6.50)	<0.001***	77.7 (10.93)	91.7 (8.42)	<0.001***

†Number (%), ‡Median (Interquartile range), *p<0.05, **p<0.01, ***p<0.001

Abbreviations*:* AD: Alzheimer's disease; ACE: Adddenbrooke's Cognitive Examination; VSTMBT: Visual Short-Term Memory Binding Task; FCSRT: Free and Cued Selective Reminding Test; HVLT: Hopkin's Verbal Learning Test; CDT: Clock Drawing Test

The two groups performed significantly different in all neuropsychological tests except for Rey Figure Copy. Controls achieved higher scores than patients in all measures except for the FCSRT cued recall, in which measure patients outscored controls (p = 0.004).

In the patient group, the mean ACE-R score decreased by 2.3% over the course of the study. In the control group, the mean ACE-R score decreased by 0.5% over the course of the study (Figure 2.3).

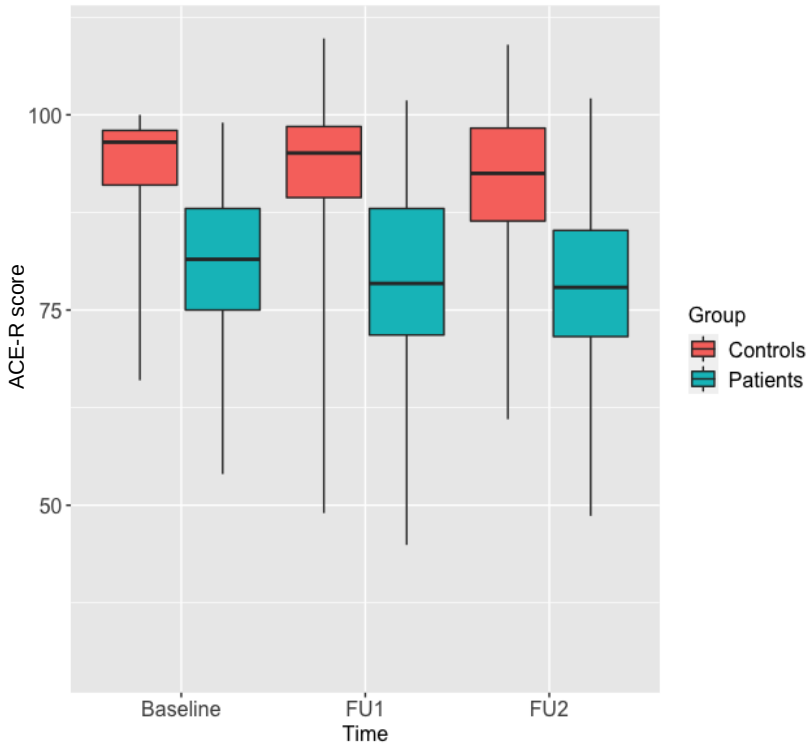

Figure 2.3: Distribution of multiply imputed ACE-R scores by group across the three study time points. *Abbreviations: ACE-R: Addenbrooke's Cognitive Examination-Revised; FU1: Follow-up 1; FU2: Follow-up 2*

Linear mixed models indicated that the change in ACE-R scores over time was statistically significant in the patient group, with an estimated decrease of 1.385 points in the ACE-R per time point. The estimated decrease of 1.097 points per time point in the control group was not statistically significant (Table 2.2). Residual plots indicated that the assumptions of linearity and homoskedasticity were met, and histograms indicated that residuals were normally distributed.

Table 2.2: Linear mixed model of time as a predictor of change in ACE-R score

Parameter	Estimate (*β*)	Standard error	*t*-value	*p*-value
Control group				
Intercept	95.157	1.185	80.299	<0.001***
Time	-1.097	0.572	-1.918	0.065
Patient group				
Intercept	81.717	1.445	56.543	<0.001***
Time	-1.385	0.556	-2.491	0.015*

*p<0.05, **p<0.01, ***p<0.001

2.4.2 Predicting decline in ACE-R performance

A linear mixed model was fitted to examine the relationship between baseline VSTMBT binding scores, FCSRT free scores, HVLT total scores, and CDT scores and change in ACE-R over time.

Residual plots and histograms indicated assumptions of linearity, homoskedasticity and normality were met. There was no evidence of multicollinearity, with a variance inflation factor of <3 for all covariates in the model.

Likelihood ratio tests showed that random slope models (subject-specific slopes for ACE scores over time) were not necessary. We therefore constructed random intercept models where individual participants' intercepts for the trajectory of their performance in the ACE-R were allowed to vary.

Linear mixed models indicated that ACE-R scores were best predicted by baseline diagnosis, time, baseline FCSRT free scores, baseline HVLT total scores and baseline CDT scores. Baseline VSTMBT binding scores did not significantly predict decline in ACE-R scores (Table 2.3).

Table 2.3: Linear mixed model of demographic, time-related, and neuropsychological predictors of change in ACE-R score

Parameter	Estimate (*β*)	Standard error	*t*-value	*p*-value
Intercept	58.821	7.406	7.942	<0.001***
Baseline age	0.001	0.070	0.011	0.991
Education	0.193	0.145	1.327	0.191
Baseline diagnosis	-4.084	1.289	-3.168	0.002**
Time	-1.250	0.407	-3.071	0.004**
VSTMBT binding	2.159	2.434	0.887	0.383
FCSRT free	0.388	0.085	4.588	<0.001***
HVLT total	0.404	0.112	3.608	0.001**
CDT	2.549	0.666	3.825	<0.001***

Abbreviations: VSTMBT: Visual Short-Term Memory Binding Task; FCSRT: Free and Cued Selective Reminding Test; HVLT: Hopkin's Verbal Learning Test; CDT: Clock Drawing Test

*p<0.05, **p<0.01, ***p<0.001

2.4.3 Predicting conversion to AD

Baseline scores in the VSTMBT, FCSRT, HVLT, and CDT for patients who did not develop AD within the study time frame compared to those who did are outlined in Figure 2.4.

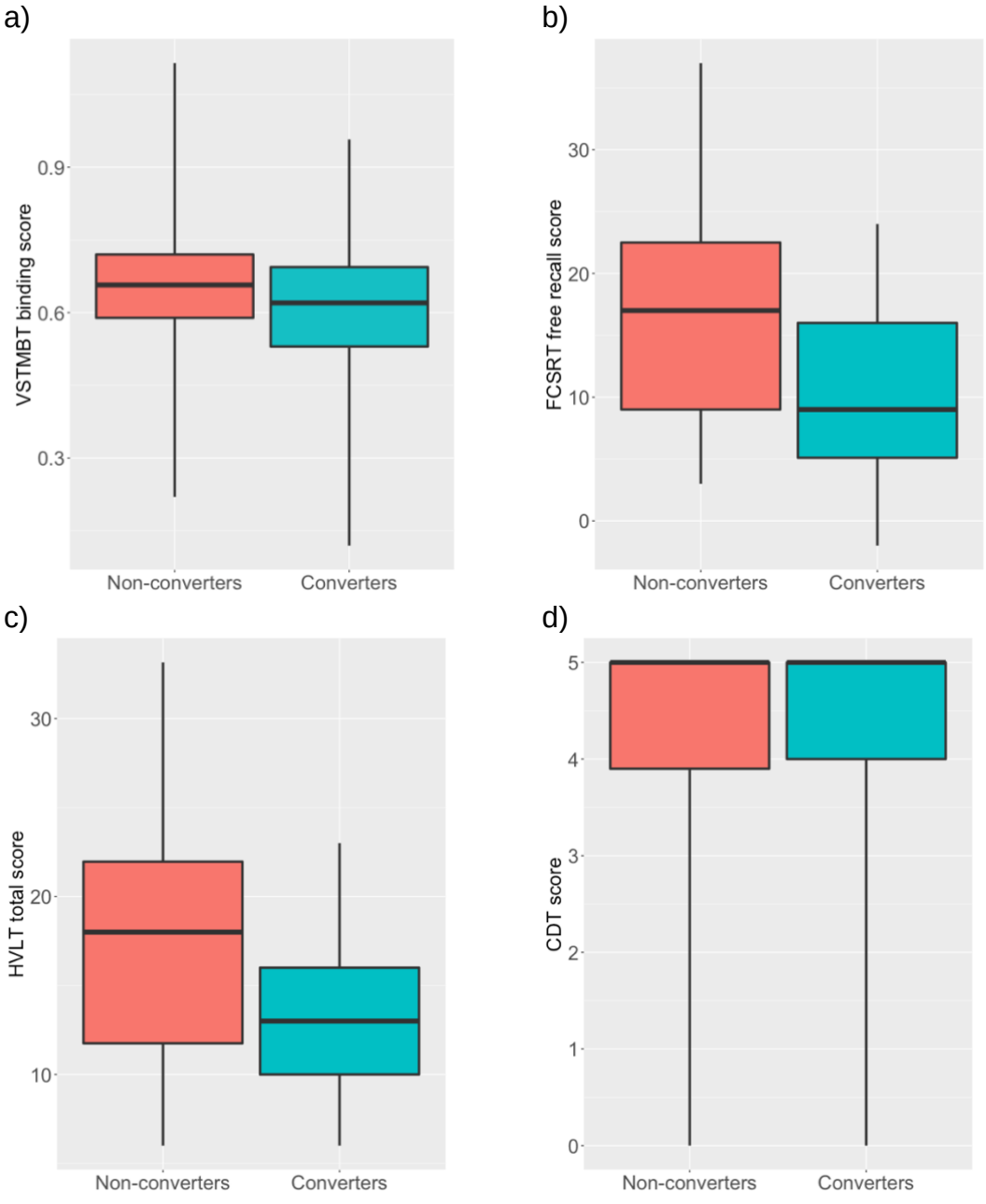

Figure 2.4: Baseline scores in a) VSTMBT binding, b) FCSRT free recall, c) the HVLT, and d) the CDT in Non-converters (Mild Cognitive Impairment, no Alzheimer's Disease) and Converters (end of study diagnosis of Alzheimer's Disease). *Abbreviations: VSTMBT: Visual Short-Term Memory Binding Task; FCSRT: Free and Cued Selective Reminding Test; HVLT: Hopkin's Verbal Learning Test; CDT: Clock Drawing Test*

A logistic regression model was fitted to statistically examine the relationship between baseline VSTMBT binding scores, FCSRT free scores, HVLT total scores, and CDT scores and conversion to AD.

The assumption of linearity was assessed by visually examining the scatter plots between the continuous predictors and the logit transformation of the dependent variable (an end of study diagnosis of AD). The scatter plots indicated that all continuous variables were linearly associated with end of study diagnosis in logit scale. For this reason, no transformations were required. As per the linear mixed model, there was no evidence of multicollinearity.

Control patients who developed AD and patients with a baseline diagnosis of MCI were included in this model (n=85). The logistic regression model was adjusted for baseline age and years of education. The model indicated that none of the baseline variables significantly predicted conversion from MCI to AD (Table 2.4).

Table 2.4: **Logistic regression model of demographic, time-related, and neuropsychological predictors of conversion from MCI to AD**

Parameter	Estimate (β)	Standard error	Exp(β)	*t*-value	*p*-value
Intercept	-0.171	3.339	0.843	-0.051	0.959
Baseline age	0.009	0.035	1.009	0.265	0.791
Education	0.119	0.070	1.126	1.699	0.089
VSTMBT binding	-1.588	2.507	0.204	-0.633	0.529
FCSRT free	-0.076	0.042	0.927	-1.831	0.067
HVLT total	-0.071	0.060	0.931	-1.181	0.238
CDT	0.202	0.260	1.224	0.775	0.439

Abbreviations: VSTMBT: Visual Short-Term Memory Binding Task; FCSRT: Free and Cued Selective Reminding Test; HVLT: Hopkin's Verbal Learning Test; CDT: Clock Drawing Test

2.4.4 Examining the construct validity of the VSTMBT

Partial correlations between VSTMBT scores and other traditional neuropsychological tests are outlined in Table 2.5. The table is organised according to the MTMM method, with tests that are expected to correlate grouped together. The correlations accounted for age and education.

The shape condition of the VSTMBT was not correlated with other measures of visual memory, indicating low convergence. This measure did correlate with the Trail Making Test B (r = -0.44, $p < 0.001$) and the Letter Fluency task (r = 0.26, $p < 0.05$), both of which primarily assess executive function. Furthermore, the shape condition of the VSTMBT also correlated with the Digit Symbol task (r = 0.32, $p < 0.01$), a test of processing speed, and the Rey Figure Copy (r = 0.38, $p < 0.01$), a test of visuospatial ability. These correlations suggest weak discriminant validity.

The binding condition of the VSTMBT was not correlated with any other test included in the analysis. The absence of a significant correlation with other measures of visual memory signifies weak construct validity. Conversely, the absence of a significant

correlation with measures of other domains is an indication of good discriminant validity.

Table 2.5: Multitrait-multimethod matrix of VSTMBT scores and traditional neuropsychological tests

		Visual memory							**Verbal memory**				**Executive function**			**Processing speed**		**Visuo-spatial ability**
		VSTMBT shape	VSTMBT binding	Rey Figure Immediate recall	Rey Figure delayed recall	FCSRT free	FCSRT cued	FCSRT total	HVLT delayed recall	HVLT delayed recog-nition	HVLT total	ACE memory index	CDT	Trail making B	Letter fluency	Trail making A	Digit symbol	Rey Figure copy
Visual memory	VSTMBT shape	1.0																
	VSTMBT binding	0.12	1.0															
	Rey Figure Immediate recall	0.21	0.15	1.0														
	Rey Figure delayed recall	0.18	0.16	0.93***	1.0													
	FCSRT free recall	0.17	-0.01	0.25*	0.27*	1.0												
	FCSRT cued recall	-0.12	0.10	-0.15	-0.12	-0.79***	1.0											
	FCSRT total	0.10	0.11	0.20	0.28*	0.57***	0.04	1.0										
Verbal memory	HVLT delayed recall	0.20	0.07	0.11	0.20	0.54***	-0.34**	0.47***	1.0									
	HVLT delayed recognition	0.13	0.15	0.09	0.19	0.45***	-0.25*	0.43***	0.56***	1.0								
	HVLT total	0.18	0.14	0.16	0.21	0.59***	-0.38**	0.54***	0.62***	0.63***	1.0							
	ACE memory index	0.20	0.11	0.21	0.27*	0.62***	-0.26	0.70***	0.45***	0.52***	0.60***	1.0						
Executive function	CDT	0.02	0.07	-0.07	-0.04	0.23	-0.20	0.12	0.15	0.06	0.13	0.23*	1.0					
	Trail making B	-0.44***	0.02	-0.07	-0.11	-0.36**	0.02	-0.60***	-0.28*	-0.38**	-0.33**	-0.37**	-0.13	1.0				
	Letter fluency	0.26*	0.06	-0.11	-0.14	0.29*	-0.25*	0.16	0.22	0.14	0.24	0.27	0.24	-0.22	1.0			
Processing speed	Trail making A	-0.18	-0.11	0.10	0.07	-0.05	-0.09	-0.23	0.14	-0.16	0.01	-0.01	-0.11	0.61***	0.01	1.0		
	Digit symbol	0.32**	0.16	0.28*	0.29*	0.52***	-0.34**	0.38**	0.18	0.30*	0.27*	0.40**	0.06	-0.57***	0.23	-0.29*	1.0	
Visuospatial ability	Rey Figure copy	0.38**	0.14	0.60***	0.57***	0.01	-0.07	-0.07	0.04	-0.01	0.05	0.02	-0.12	-0.04	0.02	0.06	0.15	1.0

Legend: Yellow: monotrait monomethod correlations; Darker red: significant monotrait-heteromethod correlations; Darker blue: non-significant monotrait-heteromethod correlations; Pale red: significant heterotrait-heteromethod correlations; Light blue: non-significant heterotrait-heteromethod correlations

Abbreviations: VSTMBT: Visual Short-Term Memory Binding Task; FCSRT: Free and Cued Selective Reminding Test; HVLT: Hopkin's Verbal Learning Test; ACE: Addenbrooke's Cognitive Examination; CDT: Clock Drawing Test.

*p<0.05, **p<0.01, ***p<0.001

2.5 Discussion

2.5.1 Summary of results

The study compared four neuropsychological tests in terms of their ability to predict cognitive decline and a diagnosis of AD in healthy individuals and individuals with MCI. As expected, performance in the FCSRT, HVLT, and CDT at baseline predicted decline in ACE-R scores over the subsequent two years, while controlling for baseline diagnosis. However, performance in the VSTMBT did not predict change in ACE-R scores over time.

None of the neuropsychological tests significantly predicted conversion from MCI to AD. The predictive ability of FCSRT did approach significance (p = 0.067), however, which suggests that, out of all measures included in the model, the FCSRT free recall task may be the most accurate in predicting AD in individuals at the MCI stage of the disease.

The psychometric analysis demonstrated that performance in the binding condition of the VSTMBT was uncorrelated with performance in a range of traditional neuropsychological tests.

2.5.2 Why did the VSTMBT not predict decline?

The non-significance of the VSTMBT in predicting change in ACE-R scores or predicting conversion from MCI to AD was unforeseen, but interesting in light of recent discussions regarding the timeline of deterioration of conjunctive binding in AD. Given the considerable body of research demonstrating conjunctive binding deficits in the preclinical stages of AD (Koppara et al., 2015; Norton et al., 2020; Parra et al., 2010), these findings warrant further examination.

A potential explanation for these results relates to the characteristics of the sample and the timing of assessment. As outlined in the introduction, evidence suggests that conjunctive binding deficits are seen at a very early stage of the disease, before any other cognitive deficits are present (Parra et al., 2010). It is becoming increasingly recognised that different cognitive tests are needed for different stages of disease progression. For example, some tests may show higher accuracy at pre-symptomatic stages whereas others may be more helpful to clarify degree of impairment at the point where deficits are beginning to impact on functioning (Hoefeijzers, Calia, & Parra, 2016). The need for differential cognitive assessment is reflected by the pattern of degeneration in the brain. Regions in sub-hippocampal areas, such as the trans-entorhinal region, have been shown to be among the first regions to degenerate (Braak stage I-II; Braak, Thal, Ghebremedhin, & Del Tredici, 2011). Damage in such regions may cause low-level deficits that are too subtle to be noticed. However, these low-level functions are the building blocks of memory. It is at this early stage that impairments in the VSTMBT have been detected (Parra et al., 2010). Conjunctive binding has been shown to recruit ventral visual pathways, which feed into sub-hippocampal regions, and thus may be one of the earliest components of memory to become impaired in AD (Parra, Della Sala, Logie, & Morcom, 2014; Staresina & Davachi, 2010).

With this in mind, it is possible that by the time an individual has progressed to an MCI stage, deficits in conjunctive binding may have floored, such that assessment of conjunctive binding with the VSTMBT no longer provides useful predictive information. In the MCI sample, the average performance in the VSTMBT binding condition was only slightly above chance (*M* = 0.635, *SD* = 0.101), suggesting that, for these individuals, the disease process had already progressed to the point that it was no longer informative to assess functions mediated by sub-hippocampal regions. In the control group, the follow-up time may not have been long enough to detect whether their VSTMBT scores at baseline predict cognitive changes or AD. Such an explanation could account for why the VSTMBT did not predict cognitive changes in this sample.

This interpretation is supported by a recent paper published by Norton and colleagues (2020), which demonstrated that conjunctive binding was related to amyloid burden in individuals who carry a gene mutation responsible for familial AD. Aggregation of amyloid in the brain is one of the earliest known indicators of AD pathology and can be seen at least a decade before any symptoms are noticeable (Braak et al., 2011; Jack et al., 2018). Aggregation of another biomarker, tau, appears to more closely coincide with onset of cognitive decline (Jack et al., 2013). Norton and colleagues (2020) found that conjunctive binding correlated higher with amyloid levels than tau levels, suggesting that impairments in conjunctive binding may appear prior to the formation of measurable levels of tau. The authors suggest that, as tau develops, conjunctive binding performance approaches a floor, weakening the relationship between conjunctive binding and tau levels. This finding suggests that assessing conjunctive binding with the VSTMBT may have the most predictive value in the early, preclinical stage of AD. At later stages of the disease, such as the MCI stage, the test may lose its predictive ability, as evidenced by the results of this study.

The suggestion that the VSTMBT has high predictive power in the preclinical stages of AD which reduces as the disease progresses has important clinical implications. The results of the present study, alongside previous research on the topic, indicate that this tool is most helpful at the point whereby an individual is still functioning at a relatively normal level. Much of the research on the VSTMBT has been carried out with participants who know they are in the preclinical stages of AD because they carry a gene mutation responsible for familial AD (Lopera et al., 1997; Parra et al., 2010). Thus, these individuals were already aware of their prognosis. However, for people who are not aware, the decision to undergo assessment that will potentially predict whether or not an individual is likely to develop AD should not be taken lightly. Careful consideration must be given to the appropriateness of such an assessment in the context of an individual's circumstances. Pre-assessment counselling akin to genetic counselling may be one such way that clinicians can ensure informed consent and facilitate preparation for possible outcomes (La Fontaine, Buckell, Knibbs, & Palfrey, 2014). These considerations are particularly important in light of growing evidence that many people and their families report feeling unprepared for the outcome of an assessment and experience significant stigma and distress when a diagnosis of MCI or dementia is given (Robinson et al., 2012).

2.5.3 Significance of traditional tests in predicting decline

The significance of the FCSRT, HVLT, and CDT in predicting decline in this sample is line with previous research (Amodeo et al., 2015; Derby et al., 2013; Hogervorst et al., 2002), and may also be discussed in the context of how the timing of these tests relates to stage of the disease. Traditional memory assessments for AD have focused on assessing higher-level hippocampal functions and are therefore aimed at measuring functioning at the point whereby AD has progressed from sub-hippocampal to hippocampal regions and beyond (Braak stage III-IV; Braak et al., 2011; Hoefeijzers et al., 2016). The FCSRT is an example of one such test. Performance in the FCSRT has been shown to correlate with hippocampal volume (Sarazin et al., 2010) and FCSRT performance is significantly impaired in patients with selective damage to the hippocampal system (Jonin et al., 2019). These findings indicate that FCSRT is likely to be a suitable assessment at the point whereby higher-level memory functions are beginning to show impairment. The results of this study support this hypothesis, as they showed that the FCSRT predicted future cognitive decline in this sample, and was the most accurate test in predicting conversion from MCI to AD.

2.5.4 Conjunctive binding as a distinct construct

The psychometric analysis indicated poor convergent validity for the VSTMBT. This analysis, however, raises interesting questions about the construct of conjunctive binding. The deviation of the binding condition of the VSTMBT from all other measures suggests that this tool may be measuring a construct distinct from those measured in traditional neuropsychological tools. The process of conjunctive binding may be regarded as a lower-level process within working memory. Once features are bound, they are regarded as one unit, as evidenced by studies which demonstrate that bound objects have no extra cost to memory load than objects with single features (Baddeley, Allen, & Hitch, 2011; Luck & Vogel, 1997). Thus, while most short-term memory tasks assess memory post-unification, the VSTMBT assess memory pre-unification. The separation of these constructs is supported by research demonstrating that brain structures relevant for conjunctive binding appear to be distinct from those responsible for encoding of unified objects (Staresina & Davachi, 2010).

Although the primary reason for carrying out a partial correlation analysis was to assess the construct analysis of the VSTMBT, this type of analysis also provides information on the construct validity of the other measures included in the correlation matrix. It is interesting to note that the FCSRT free recall and total score showed greater overlap with measures of verbal memory than measures of visual memory. The task draws on both visual and verbal memory, but this result suggests that the FCSRT may be a stronger measure of verbal memory. The FCSRT free recall also correlated with non-memory tasks, including the Trail Making Test B, Letter Fluency, and Digit Symbol, suggesting poor discriminative validity for measuring memory. This finding contrasts with previous research on the construct validity of the FCSRT (Clerici et al., 2017).

2.5.5 Limitations

One of the most significant limitations of this study was the poor retention of participants over the course of the study period, with a dropout rate of 38% at the first

follow-up assessment and 69% at the second follow-up assessment. This resulted in a significant amount of missing data. Without information about missing data, it is impossible to verify the reasons for missingness. However, participants with a diagnosis of MCI were less likely to return for follow-up than control participants, which suggests that dropout may be related to increasing disability. Furthermore, individuals who were more impaired may have been less able to engage in the full battery of tests at baseline. These explanations would suggest that missing data are missing not at random (MNAR), which is an issue for many longitudinal studies (Ibrahim & Molenberghs, 2009). When data are MNAR, this can lead to an unrepresentative sample and, as a result, biased data (Heymans & Eekhout, 2019). Inferences made on the basis of such data may be significantly compromised as a result. There are currently no existing methods of handling MNAR data appropriately and as a result, the use of multiple imputation where it is plausible that data are MNAR is questioned by some (Jakobsen, Gluud, Wetterslev, & Winkel, 2017).

Multiple imputation, whereby observed data is used to predict missing data, is based on the assumption that data are missing at random (MAR). As it is impossible to ascertain whether data are MAR or MNAR, the assumption of data being MAR is generally accepted as a working assumption in practice (Heymans & Eekhout, 2019). For this reason, multiple imputation was used in this study. This means, however, that if the observed data were biased, the imputed data will also be biased. Given that a higher proportion of patients dropped out than controls, it is plausible that the observed, and therefore, the imputed data were biased.

Furthermore, although there is a lack of consensus on whether or not multiple imputation should be carried out when the proportion of missing data is large, some have suggested that, when more than 40% of the data is missing, any outcomes should be considered as hypothesis generating only (Jakobsen et al., 2017). According to this rule of thumb, the outcome of the linear mixed model analysis, which compared the VSTMBT, FCSRT, HVLT and CDT in terms of their ability to predict decline in ACE-R performance, should be interpreted tentatively.

A further limitation of the study is that the data were collected by multiple researchers across multiple locations at different time points. Theoretically, the role of the researcher in quantitative studies is insubstantial, with participants contribution seen as distinct from any influence from the researcher (Simon, 2011). However, this idea has been questioned by those who argue that the researcher's background and position can potentially impact all aspects of the research study, including the topic choice, data collection and interpretation (Field & Derksen, 2021). Therefore, while administration of neuropsychological assessments is standardised, variation may be introduced if the manner in which a measure is administered varies across examiners, location, or time point. Such variation lowers the reliability and validity of the measures and may introduce bias to the data (Stebbins, 2007). Furthermore, variability may also be introduced by the fact that the author of the present study was not involved in data collection and therefore could not take into account any observations or potential subtleties that may have been picked up by the primary researcher during data collection.

Another potential weakness of this study is that the patient and control groups were not matched by education, with the control group reporting significantly more years of

education than the patient group. As many traditional neuropsychological assessments are influenced by education level (Costa et al., 2017), this difference may have led to inaccurate outcomes. Years of education was included as a covariate in the analyses in order to reduce confounding as much as possible. However, this method is less statistically precise than matching (Pearce, 2016) and, correspondingly, the discrepancy may somewhat bias the results.

Finally, in the current study, 44% of participants with MCI developed AD over approximately two years, irrespective of dropout. Practice guidelines for MCI published in 2018 reported a conversion rate of 15% over the same time frame (Petersen et al., 2018). The reasons for much higher rate of conversion to AD in the current study sample are unclear but may indicate a potential sampling error due to how participants were recruited and selected, which can result in an unrepresentative sample.

This study highlights the challenges associated with accurately examining neuropsychological measures over time in a population of older participants who may have physical co-morbidities as well as cognitive impairment and, furthermore, may lack capacity to consent (Grill et al., 2019). European consensus papers have suggested that potential solution to this problem may be to link up cohort studies in order to analyse data on a larger scale (Costa et al., 2017; Maruta et al., 2011). Harmonisation of tools and procedures across Europe is a key part in forming common datasets and achieving more reliable and generalisable results.

2.5.6 Conclusions and recommendations

The results of the present study indicate that, while VSTMBT performance is impaired in individuals with MCI, it does not predict decline in cognitive function over the course of two years in healthy individuals and individuals with MCI, in contrast to traditional neuropsychological assessments. Furthermore, the results indicate that the VSTMBT does not predict conversion from MCI to AD.

These findings support the emerging idea that conjunctive binding is one of the earliest cognitive markers of AD, with high predictive ability in the early stages of the disease that declines as the disease progresses. Further research is required to explore this hypothesis in more detail. Such research should ideally follow individuals who are cognitively unimpaired in all domains other than conjunctive binding over a long period of time to assess the predictive value of this early marker.

The findings of this study provide support for the idea that neuropsychological assessment of AD should be appropriately matched to the stage of the disease and the purpose of the assessment. Assessments of conjunctive binding, such as the VSTMBT may be most useful in the preclinical stages of AD, whereas assessments of relational binding, such as the FCSRT, may be most useful in the early stages of the AD clinical syndrome.

Future research should give careful consideration to methodology, in light of the limitations highlighted in the present study. For example, longitudinal studies should consider maximising efforts to increase retention of participants over time (Grill et al., 2019). Another potential consideration for future research could be to record

information about time to diagnosis, in order to carry out a survival analysis. Such an analysis may be able to provide more accurate predictive information relating to the development of AD (Tian et al., 2003).

The study also demonstrated that the binding condition of the VSTMBT does not correlate with traditional dementia assessments. This finding suggests that the underlying construct assessed by the VSTMBT is distinct from those assessed by traditional neuropsychological tests. Further research is required to explore the neuroanatomical correlates of this construct and to investigate how this construct is affected by AD pathology in the preclinical stages of the disease.

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Appendices

Appendix A: Journal guidelines for Journal of Neuropsychology

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Sections

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-

The following types of paper are invited:

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Please provide appropriate keywords.

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Author Guidelines updated 14th October 2019

Appendix B: PRISMA checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	8
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	9
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	12
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	12
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	12
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	13
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	12
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	12
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	13
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	13
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	13
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	13-14
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	14

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I2) for each meta-analysis	14-15
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	14-15
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	16-17
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	19-26
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	28
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	19-26
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	31-36
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression [see item 16])	35-36
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	36-38
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	38-39
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	39-40
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	

Appendix C: Table outlining reasons for exclusion for articles excluded at full-text review

	Title	Author	Year	Reason for exclusion
1	The Prueba Cognitiva de Leganés is a valid screening tool for diagnosing dementia in people with low educational level.	Prince	2004	Commentary
2	Cognitive deficits in African Americans with diabetes in an emergency department.	Rovner et al.	2020	Commentary
3	Prevalence and subtypes of dementia in Taiwan: A community survey of 5297 individuals	Liu et al.	1995	Full text not available
4	Literacy and Performance on the Mini-Mental State Examination	Weiss et al.	1995	Full text not available
5	Mini-Mental Status Examination: is it appropriate for screening in Thai elderly?	Jitapunkul &Lailert	1997	Full text not available
6	Validity of clinical use of the clock-drawing test in Thai elderly patients with memory problems	Jitapunkul et al.	2000	Full text not available
7	Cognitive function of 320 people over 65 years from longevous areas in Guangxi Zhuang Autonomous Region: Feasibility of the mini-mental state examination	Wu et al.	2006	Full text not available
8	First Spanish version of the French test Rapid Assessment of Cognitive Functions (Gil et al, 1986). Adaptation and validation in a geriatric sample	Arroyo-Anlló et al	2009	Full text not available
9	Nutritional deficiency in early life facilitates aging-associated cognitive decline	Kang et al.	2017	Full text not available
10	Factors associated with cognitive performance in elderly caregivers	Pavarini et al.	2018	Full text not available
11	Correlation between systolic blood pressure and cognitive impairment in people aged 70 years and above: A cross-sectional survey based in a rural area of Xi'an, China	Shang et al.	2020	Full text not available
12	The Mini-Mental State Examination in a general population: impact of educational status	Bertolucci et al.	1994	Full text not published in English
13	The Mini-Mental State Examination in an outpatient population: Influence of literacy.	Bertolucci et al.	1994	Full text not published in English
14	Mini Mental State Examination: association of the score obtained with the age and degree of literacy in an aged population	Pi et al.	1994	Full text not published in English
15	Influences of age and education in the Mini Mental State Examination in a Spanish speaking population	Ostrosky-Solis et al.	1999	Full text not published in English

16	The mini-mental state examination in the Chinese residents population aged 55 years and over in the urban and rural areas of Beijing	Zhang & Hong	1999	Full text not published in English
17	The prevalence of dementia and its main subtypes in subjects older than 65 years: impact of occupation and education. The Toledo Study	Garcia Garcia et al.	2001	Full text not published in English
18	Applicability of the MMSE in west China: Who is more suitable?	Luo et al.	2002	Full text not published in English
19	Concordance among Mini-Examen Cognoscitivo and Mini-Mental State Examination in cognitive impairment screening	Vinyoles Bargallo et al.	2002	Full text not published in English
20	Applicability of the Chinese version of the Mini-Mental State Examination in the screening of Alzheimer's disease in rural areas of China.	Wu et al.	2002	Full text not published in English
21	Detection of cognitive impairment in the population of persons older than 64 years: First phase of the ciuda'1 project	Limon Ramirez et al.	2003	Full text not published in English
22	The prevalence of mild cognitive impairment among residents aged 55 or over in Chengdu area	Qiu et al.	2003	Full text not published in English
23	Suggestions for utilization of the mini-mental state examination in Brazil	Brucki et al.	2003	Full text not published in English
24	Mini-mental state examination in community-dwelling elderly: preliminary data from Santo Antonio de Padua, Rio de Janeiro, Brazil	Laks et al.	2003	Full text not published in English
25	The photo test	Carnero-Pardo & Montoro-Rios	2004	Full text not published in English
26	Factors influencing depressive symptoms and cognitive disorders among elderly.	Ilhan et al.	2006	Full text not published in English
27	Use of the Mini-Cog test as a screening method for dementia in the Italian population: the Argento Study results	Michieletto et al.	2006	Full text not published in English
28	A survey of mental health among 318 cases of elderly persons aged over 65 years in Bama macrobiotic area of Guangxi	Wu et al.	2006	Full text not published in English
29	Screening results of the cognitive function of the elderly from Jiazhuan of Bama County in Guangxi Zhuang Autonomous Region	Wu et al.	2006	Full text not published in English
30	The performance pattern of normal illiterate and patients with early Alzheimer's disease on the semantic association of verbal fluency test.	Chung et al.	2007	Full text not published in English

31	Analysis and characterization of functional capacity and mental state in residents in old folk's home	Converso et al.	2007	Full text not published in English
32	Prevalence of dementia in the elderly aged above 65 in a district in the Basque country	Fernez Martinez et al.	2008	Full text not published in English
33	Analysis of cognitive impairment and associated factors of the elderly in Shanghai suburbs	Tang et al.	2008	Full text not published in English
34	Assessment of episodic memory in illiterate elderly	Dessi et al.	2009	Full text not published in English
35	Cognitive impairment and risk factor survey in patients with ischemic stroke in Beijing communities	Liu et al.	2009	Full text not published in English
36	Survey on cognitive function and analysis of associated factors among elders in Shanghai suburb	Yao et al.	2009	Full text not published in English
37	Cognitive function in menopausal women evaluated with the Mini-Mental State Examination and Word-List Memory Test	Fernandes et al.	2009	Full text not published in English
38	Study on the incidence and risk factors of dementia in elderly residents from communities in Beijing	Wu et al.	2010	Full text not published in English
39	Education, age, and cognitive impairment of elderly residents in long-term institutions	Domiciano et al.	2014	Full text not published in English
40	Mini Mental State Examination (MMSE): determination of cutoff scores according to age and educational level	Solias et al.	2014	Full text not published in English
41	Cognitive decline: Prevalence and correlates in a rural ecuadorian community. lessons from the atahualpa project	Brutto et al.	2017	Full text not published in English
42	Prevalence of Alzheimer's disease and other dementias in rural India: The Indo-US study	Chandra et al.	1998	Literate and illiterate groups not specified/differentiated
43	Reading ability, education, and cognitive status assessment among older adults in Harlem, New York City	Albert et al.	1999	Literate and illiterate groups not specified/differentiated
44	Comparison of the Clock Test and a questionnaire-based test for screening for cognitive impairment in Nigerians	VerJagt et al.	2006	Literate and illiterate groups not specified/differentiated
45	Penn State screen exam for the detection of frontal and temporal dysfunction syndromes: Application to ALS	Flaherty-Craig et al.	2009	Literate and illiterate groups not specified/differentiated
46	A population-based study of cognitive function in older people with subjective memory complaints.	Benito-Leon et al.	2010	Literate and illiterate groups not specified/differentiated
47	Feasibility of using everyday abilities scale of India as alternative to mental state examination as a screen in two-phase survey estimating the prevalence of dementia in largely illiterate Indian population	Cher et al.	2016	Literate and illiterate groups not specified/differentiated

48	The MMSE and MoCA for Screening Cognitive Impairment in Less Educated Patients with Parkinson's Disease	Kim et al.	2016	Literate and illiterate groups not specified/differentiated
49	Validation of TICS for detection of dementia and mild cognitive impairment among individuals characterized by low levels of education or illiteracy: a population-based study in rural Greece	Georgakis et al.	2017	Literate and illiterate groups not specified/differentiated
50	How to Assess Executive Functions in a Low-Educated and Multicultural Population Using a Switching Verbal Fluency Test (the TFA-93) in Neurodegenerative Diseases?	Narme et al.	2019	Literate and illiterate groups not specified/differentiated
51	Assessing feasibility of a focused geriatric assessment in older adults with sickle cell disease to address functional risk factors for morbidity and mortality	Oyedeji et al.	2019	Literate and illiterate groups not specified/differentiated
52	Comparison between two tests of delayed recall for the diagnosis of dementia	Takada et al.	2005	Not a screening test
53	Analysis of brief language tests in the detection of cognitive decline and dementia.	Radanovic et al.	2007	Not a screening test
54	Incidence and subtypes of dementia in three elderly populations of central Spain	Bermejo-Pareja et al.	2008	Not a screening test
55	A nationwide survey on the prevalence of dementia and mild cognitive impairment in South Korea	Kim et al.	2011	Not a screening test
56	Epidemiological study and risk factors of stroke in assiut governorate, Egypt: Community-based study	Khedr et al.	2013	Not a screening test
57	Socio-demographic determinants of mental health problems among rural elderly population	Kumar et al.	2013	Not a screening test
58	Prevalence of ischemic and hemorrhagic strokes in Qena governorate, Egypt: Community-based study	Khedr et al.	2014	Not a screening test
59	Translation and validation of Chinese version of the Problems in Everyday Living (PEDL) test in patients with mild cognitive impairment	Law et al.	2014	Not a screening test
60	Prevalence of mild cognitive impairment and dementia among the elderly population of qena governorate, upper Egypt: A community-based study	Khedr et al.	2015	Not a screening test
61	Prevalence of Parkinsonism and Parkinson's disease in Qena governorate/Egypt: A cross-sectional community-based survey	Khedr et al.	2015	Not a screening test

62	Intersecting pentagons as surrogate for identifying the use of mini mental state examination in assessment of dementia in a largely illiterate population	Raina et al.	2015	Not a screening test
63	Perceptions of precision medicine among diverse dementia caregivers and professional providers	Gaugler et al.	2019	Qualitative study
64	Effects of literacy on semantic verbal fluency in an immigrant population.	Nielsen et al.	2016	Sample overlap with included study
65	One Size Does Not Fit All: Comparative Diagnostic Accuracy of the Rowland Universal Dementia Assessment Scale and the Mini Mental State Examination in a Memory Clinic Population with Very Low Education	Goudsmit et al.	2018	Sample overlap with included study
66	Incidence and subtypes of dementia in southern Taiwan. Impact of socio- demographic factors	Liu et al.	1998	Scores for literate and illiterate participants not compared or reported separately
67	Screening for impaired cognitive function among the elderly in Spain: reducing the number of items in the Short Portable Mental Status Questionnaire	Gornemann et al.	1999	Scores for literate and illiterate participants not compared or reported separately
68	Development of simple cognitive function measures in a community dwelling population of elderly in Spain.	Zunzunegui et al.	2000	Scores for literate and illiterate participants not compared or reported separately
69	The Bangla adaptation of Mini-Mental State Examination (BAMSE): an instrument to assess cognitive function in illiterate and literate individuals.	Kabir et al.	2000	Scores for literate and illiterate participants not compared or reported separately
70	Epidemiologic survey of dementia in a community-dwelling Brazilian population	Herrera et al.	2002	Scores for literate and illiterate participants not compared or reported separately
71	Prevalence of dementia in a semi-urban population in Sri Lanka: Report from a regional survey	De Silva et al.	2003	Scores for literate and illiterate participants not compared or reported separately
72	Simplifying detection of cognitive impairment: Comparison of the Mini-Cog and Mini-Mental State examination in a multiethnic sample	Borson et al.	2005	Scores for literate and illiterate participants not compared or reported separately
73	Prevalence of cognitive and functional impairment in community-dwelling elderly: Importance of evaluating activities of daily living	Laks et al.	2005	Scores for literate and illiterate participants not compared or reported separately

74	Performance in Luria's fist-edge-palm test according to educational level	Nitrini et al.	2005	Scores for literate and illiterate participants not compared or reported separately
75	Influence of age and schooling on the performance in a modified mini-mental state examination version - A study in Brazil northeast	de Rito-Marques et al.	2005	Scores for literate and illiterate participants not compared or reported separately
76	Diagnostic accuracy of the Eurotest for dementia: A naturalistic, multicenter phase II study	Carnero-Pardo et al.	2006	Scores for literate and illiterate participants not compared or reported separately
77	Mini-Mental State Examination: psychometric characteristics in elderly outpatients	Lourenco & Veras	2006	Scores for literate and illiterate participants not compared or reported separately
78	Sex differences in cognition among illiterate Bangladeshis: A comparison with literate Bangladeshis and Swedes	Herlitz & Kabir	2006	Scores for literate and illiterate participants not compared or reported separately
79	Life course socioeconomic disadvantage and cognitive function among the elderly population of seven capitals in latin America and the Caribbean	Nguyen et al.	2008	Scores for literate and illiterate participants not compared or reported separately
80	Subjective memory impairment in a rural population with low education in the Amazon rainforest: An exploratory study	Brucki & Nitrini	2009	Scores for literate and illiterate participants not compared or reported separately
81	Oral language comprehension assessment among elderly: A population based study in Brazil	de Araújo Carvalho et al.	2009	Scores for literate and illiterate participants not compared or reported separately
82	Cambridge Cognitive Examination: performance of healthy elderly Brazilians with low education levels	Moreira et al.	2009	Scores for literate and illiterate participants not compared or reported separately
83	Education does not equally influence all the mini mental state examination subscales and items: Inferences from a Brazilian community sample	Laks et al.	2010	Scores for literate and illiterate participants not compared or reported separately
84	Validation of the literacy independent cognitive assessment	Choi et al.	2011	Scores for literate and illiterate participants not compared or reported separately

85	Montreal cognitive assessment in detecting cognitive impairment in chinese elderly individuals: A population-based study	Lu et al.	2011	Scores for literate and illiterate participants not compared or reported separately
86	Prevalence of dementia in elderly clients of a private health care plan: A study of the FIBRA-RJ, Brazil	Correa Ribeiro et al.	2013	Scores for literate and illiterate participants not compared or reported separately
87	Applicability of the MoCA-S test in populations with little education in Colombia	Gomez et al.	2013	Scores for literate and illiterate participants not compared or reported separately
88	Reliability and validity of the short form of the literacy-independent cognitive assessment in the elderly	Kim et al.	2013	Scores for literate and illiterate participants not compared or reported separately
89	A composite score for Dokuz Eylul Cognitive state neurocognitivetest battery: A door-to-door survey study with illiterate, low and high educated elderly in Turkey	Kurt et al.	2014	Scores for literate and illiterate participants not compared or reported separately
90	Association of perceived health and depression with older adults' subjective memory complaints: Contrasting a specific questionnaire with general complaints questions.	Montejo et al.	2014	Scores for literate and illiterate participants not compared or reported separately
91	Normative study of the literacy independent cognitive assessment in illiterate and literate elderly Koreans	Kang et al.	2015	Scores for literate and illiterate participants not compared or reported separately
92	Mini-Mental State Examination in Elderly Chinese: A Population-Based Normative Study	Li et al.	2016	Scores for literate and illiterate participants not compared or reported separately
93	Optimal Cutoff Scores for Alzheimer's Disease Using the Chinese Version of Mini-Mental State Examination among Chinese Population Living in Rural Areas	Yang et al.	2016	Scores for literate and illiterate participants not compared or reported separately
94	Sundown syndrome and symptoms of anxiety and depression in hospitalized elderly.	Barros Silva et al.	2017	Scores for literate and illiterate participants not compared or reported separately
95	The TMA-93: A New Memory Test for Alzheimer's Disease in Illiterate and Less Educated People	Maillet et al.	2017	Scores for literate and illiterate participants not compared or reported separately

96	Cognitive impairment in rural elderly population in ecuador	Wong-Achi et al.	2017	Scores for literate and illiterate participants not compared or reported separately
97	Diagnosing dementia in lower educated older persons: Validation of a Brazilian portuguese version of the Rowland universal dementia assessment scale (RUDAS)	De Araujo et al.	2018	Scores for literate and illiterate participants not compared or reported separately
98	Prevalence and factors associated with mild cognitive impairment among Chinese older adults with depression	Li et al.	2018	Scores for literate and illiterate participants not compared or reported separately
99	Prevalence of and risk factors for cognitive impairment among elderly without cardio-and cerebrovascular diseases: A population-based study in rural China	Ren et al.	2018	Scores for literate and illiterate participants not compared or reported separately
100	Putative Dementia Cases Fluctuate as a Function of Mini-Mental State Examination Cut-Off Points	Rosa et al.	2018	Scores for literate and illiterate participants not compared or reported separately
101	Prevalence study of cognitive impairment and its associated sociodemographic variables using mini-mental status examination among elderly population residing in field practice areas of a medical college.	Patel et al.	2018	Scores for literate and illiterate participants not compared or reported separately
102	Psychometric evaluation of the persian version of illustrated memory impairment screen (PIMIS) test in elderly patients with Alzheimer's disease in Iran	Davoudkhani et al.	2019	Scores for literate and illiterate participants not compared or reported separately
103	The validity and reliability of a persian version of the brief community screening instrument for Dementia in the elderly patients with dementia in Iran	Davoudkhani et al.	2019	Scores for literate and illiterate participants not compared or reported separately
104	Validity and reliability of bayer activities of daily living (bayer- adl) scale in the iranian elderly dementia population: Is there distinguish between illiterate and literate demented in functional dependency?	Fadayevatan et al.	2019	Scores for literate and illiterate participants not compared or reported separately
105	Assessment of Visual Association Memory in Low-Educated, Non-Western Immigrants with the Modified Visual Association Test	Franzen et al.	2019	Scores for literate and illiterate participants not compared or reported separately
106	Related factors of cognitive impairment in community-dwelling older adults in Beijing Longitudinal Study of Aging	Han et al.	2019	Scores for literate and illiterate participants not compared or reported separately

107	MoCA Test: normative and diagnostic accuracy data for seniors with heterogeneous educational levels in Brazil	Cesar et al.	2019	Scores for literate and illiterate participants not compared or reported separately
108	Cognitive ageing trajectories and mortality of Chinese oldest-old	Hu et al.	2019	Scores for literate and illiterate participants not compared or reported separately
109	A model of cognitive evaluation battery for diagnosis of mild cognitive impairment and dementia in educated and illiterate Egyptian elderly people	Elbedewy & Elokl	2020	Scores for literate and illiterate participants not compared or reported separately
110	Preoperative assessment of cognitive function and risk assessment of cognitive impairment in elderly patients with orthopedics: a cross-sectional study.	Shuyuan et al.	2020	Scores for literate and illiterate participants not compared or reported separately
111	Applicability of SPMSQ in illiterate outpatients in clinics: The validity and reliability of the Short Portable Mental Status Questionnaire	Kojaie-Bidgoli et al.	2020	Scores for literate and illiterate participants not compared or reported separately
112	Usefulness of clock-drawing test in Indian older adults with diabetes mellitus	Tripathi et al.	2020	Scores for literate and illiterate participants not compared or reported separately
113	Cognitive deficit, physical frailty, hospitalization and emergency department visits in later life	Wang et al.	2021	Scores for literate and illiterate participants not compared or reported separately
114	Developing and testing a South African brief cognitive score in literate and illiterate people of mixed language groups	Schutte et al.	2021	Scores for literate and illiterate participants not compared or reported separately
115	Sensitivity and specificity of the mini-mental state examination in a Spanish-speaking population	Ostrosky-Solis et al.	2000	Unsuitable age range
116	Cognitive evolution by MMSE in poststroke patients	da Costa et al.	2010	Unsuitable age range
117	Distinct patterns of cognitive aging modified by education level and gender among adults with limited or no formal education: A normative study of the mini-mental state examination	Xie et al.	2015	Unsuitable age range
118	Prevalence and predisposing factors for cognitive dysfunction following adult cardiac surgery	Ziyaeifard et al.	2017	Unsuitable age range
119	Development of neuropsychological evaluation screening tool: An education-free cognitive screening instrument	Chopra et al.	2018	Unsuitable age range

120	The influence of education on performance of adults on the Clock Drawing Test.	de Noronha et al.	2018	Unsuitable age range
121	Jidong cognitive impairment cohort study: Objectives, design, and baseline screening	Song et al.	2020	Unsuitable age range
122	Prevalence of mild cognitive impairment is higher in hypertensive population: a cross-sectional study in less developed northwest China	Heizhati et al.	2020	Unsuitable age range

Appendix D: Journal guidelines for Archives of Clinical Neuropsychology

Instructions to authors

Please note that the journal requires authors to complete their copyright licence to publish form online

Manuscripts for *Archives of Clinical Neuropsychology* should be submitted online. Once you have prepared your manuscript according to the instructions below, please visit the online submission website. Use the Web site to upload your files both as individual word-processing and graphics files, and as a single PDF with graphics included. Instructions on submitting your manuscript online can be viewed here.

Please read these instructions carefully and follow them strictly. In this way you will help ensure that the review and publication of your paper are as efficient and quick as possible. The editors reserve the right to return manuscripts that are not in accordance with these instructions. Papers must be clearly and concisely written in English.

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In addition, *Archives of Clinical Neuropsychology* is offering an open access option for authors who wish to make their papers freely available online immediately. Please see the Open Access Option section below for more information.

Scope and Policy of Archives of Clinical Neuropsychology

Archives of Clinical Neuropsychology, the official journal of the National Academy of Neuropsychology, publishes original contributions dealing with psychological aspects of the etiology, diagnosis, and treatment of disorders arising out of dysfunction of the central nervous system.

The journal will also consider manuscripts involving the established principles of the profession of Neuropsychology: *(a) delivery and evaluation of services, (b) ethical and legal issues, (c) approaches to education and training.*

Preference will be given to empirical reports and key reviews. Brief research reports and commentaries on published articles (not exceeding two printed pages) will also be considered. At the discretion of the editor, rebuttals to commentaries may be in invited. Occasional papers of a theoretical nature will be considered.

The primary criterion for acceptance is scientific quality. Papers should avoid excessive use of abbreviations or jargon and should be intelligible to as wide an audience as possible. Particular attention should be paid to the Abstract, Introduction, and Discussion sections, which should clearly draw attention to the novelty and significance of the data reported. Failure to do this may result in delays in publication or rejection of the paper.

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Dr. Gregory P. Lee, PhD, Department of Neuropsychology, Barrow Neurological Institute, 222 W. Thomas Rd., Suite 315, Phoenix, AZ 85013, USA. e-mail: glee@augusta.edu

Deputy Editor

Dr. Mike R. Schoenberg, PhD, Department of Neurosurgery & Brain Repair, University of South Florida Morsani College of Medicine, South Tampa Center, 2 Tampa General Circle, Tampa, FL 33606, USA. e-mail: mschoenb@health.usf.edu

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Danielle E. Eagan, PhD, Department of Neuropsychology, Barrow Neurological Institute, 222 W. Thomas Rd., Suite 315, Phoenix, AZ 85013, USA. e-mail: Danielle.Eagan@DignityHealth.org

Article Types

The following categories of article are considered for publication in *Archives of Clinical Neuropsychology*:

- original empirical article
- brief empirical report
- book review
- test review
- literature review
- commentary
- case report

Reporting Guidelines

Responsible reporting of research studies, which includes a complete, transparent, and accurate account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. The *Archives of Clinical Neuropsychology* supports initiatives aimed at improving the reporting of health research. To accomplish this, we are asking authors to use the following reporting guideline checklists when drafting and submitting their manuscripts.

Please refer to the following article for further information about the guidelines and the rationale for them: Lee, G.P. and Schoenberg, M.R. (2017). Improving the quality of clinical neuropsychological research: Mandatory use of reporting guidelines. *Archives of Clinical Neuropsychology*, 32(6), 631-651.

Once you have completed this checklist, please save a copy and upload it as part of your submission. When requested to do so as part of the upload process, please select the file type: Reporting Guidelines Checklist. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

- *Observational Studies. Archives of Clinical Neuropsychology* requires the STROBE checklists for cohort, case-controlled, and cross-sectional studies and all observational studies of human subjects as well as case series, pilot studies, and retrospective data collection studies. Please make note on this checklist which page numbers of the manuscript include the requested information.
- *Systematic Review or Meta-analyses*. Authors reporting systematic review or meta-analysis of *randomized trials* must submit the PRISMA (previously named QUOROM) statement. Authors using the PRISMA checklist should also include a PRISMA flow diagram as Figure 1 of the submitted manuscript.

Authors reporting *meta-analyses* of *observational studies* must submit the MOOSE checklist which may be obtained in the Stroup, et al. (2000) reference below or by requesting it from the editors of *Archives of Clinical Neuropsychology*.

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- *Diagnostic Accuracy*. Authors reporting studies of the accuracy of diagnostic tests should provide the completed STARD checklist. Authors must also provide a flow diagram as Figure 1 of the submitted manuscript. The STARD checklist is available.
- *Qualitative Research*. Authors submitting studies using qualitative methods should include the SRQR (formally known as COREQ) checklist as part of their submission to the journal. The SRQR checklist may be obtained in the O'Brien, et al. (2014) reference below or in *Archives of Clinical Neuropsychology*, 2017, volume 32, issue number 5.
- *Case Reports*. Authors submitting reports on single case studies must complete the CARE checklist and include the checklist with the submitted manuscript. The CARE checklist is available at: http://www.care-statement.org/
- *Randomized Controlled Trials*. Authors reporting the results of randomized controlled trials must submit a CONSORT checklist and flow diagram. Authors must also provide a flow diagram as Figure 1 of the submitted manuscript. Authors of uncontrolled, pilot trials are not required to complete the CONSORT checklist or flow diagram.

Reference

Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D.…Thacker, S.B. (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Journal of the American Medical Association*, 283(15), 2008-2012.

Conflicts of interest

At the point of submission, *Archives of Clinical Neuropsychology* policy requires that each author reveal any financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated—including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships, or direct academic competition. When considering whether you should declare a conflicting interest or connection please consider the conflict of interest test: Is there any arrangement that would embarrass you or any of your co-authors if it was to emerge after publication and you had not declared it?

As part of the online submission process, Corresponding authors are required to confirm whether they or their co-authors have any conflicts of interest to declare, and to provide details of these. It is the Corresponding author's responsibility to ensure that all authors adhere to this policy. Examples of potential conflicts of interest which should be disclosed include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Potential conflicts of interest should be disclosed at the earliest possible stage and if the manuscript is accepted, conflict of interest information will be communicated in a statement in the published paper.

Hazards and Human or Animal Subjects

If the work involves chemicals, procedures or equipment that have any unusual hazards inherent in their use, the author must clearly identify these in the manuscript. If the work involves the use of animal or human subjects, the author should ensure that the manuscript contains a statement that all procedures were performed in compliance with relevant laws and institutional guidelines and that the appropriate institutional committee(s) have approved them. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

Preparation of Manuscripts

Manuscripts should be prepared carefully according to the *American Psychological Association Manual of Style* (6th ed). The most important rule of good style is to be consistent throughout a manuscript. Manuscripts accepted for publication must conform strictly to these style guidelines, and the editor reserves the right to make appropriate changes. If a manuscript is not in suitably usable condition, the editor reserves the right to postpone or refuse publication or request retyping.

Italics are not to be used for expressions of Latin origin, for example, in vivo, et al., per se. Use decimal points (not commas); use a space for thousands (10 000 and above). Please avoid full justification, i.e., do not use a constant right-hand margin. Ensure that each new paragraph is clearly indicated. Present tables and figure legends on separate pages at the end of the manuscript. If possible, consult a recent issue of the journal to become familiar with layout and conventions. Number all pages consecutively.
Manuscripts should be in their final form when they are submitted, so that proofs require only correction of typographical errors. All parts of the manuscript (except figures) should be double-spaced throughout and should be in a word-processing file.

Sections of the manuscript

Manuscripts should be subdivided into the following sequence of sections:

- Title page
- Structured Abstract
- Keywords
- Introduction
- Methods
- Results
- Discussion
- Funding
- Acknowledgements
- References
- Tables
- Legends to figures
- Figures (if not in a graphic-type file like PDF, tif, eps, etc.)
- Supplementary data

Length of manuscript

While papers may be of any length required for the concise presentation and discussion of the data, succinct and carefully prepared papers are favored both in terms of impact as well as in readability.

The Brief Report format may be appropriate for empirically sound studies that are limited in scope, contain preliminary, novel findings that need further replication, or represent replications and extensions of prior published work. A maximum of 2,500 words (not including abstract, tables, figures, or references) and a 150 word abstract, with a maximum of two tables or two figures, or one table and one figure, and 20 references is permitted.

General format

All sections of the manuscript must be double-spaced. Margins of 1 inch should be left at the sides, top, and bottom of each page. Number each page centered at the bottom (Title Page is 1). Italicize words and letters to appear in italics. Clearly identify unusual or handwritten symbols and Greek letters. Differentiate between the letter O and zero, and the letters I and l and the number 1. Each table and figure must be called out in the text.

Title page

The title should be short, specific, and informative. The first name, initial(s), and surname of each author should be followed by his or her department, institution, city with postal code, and country at the time the work was conducted. Email address, phone and fax numbers of the corresponding

author should also be provided. Any changes of address may be given in numbered footnotes. The author to whom proofs and reprints should be addressed should be indicated. Please provide a running title of not more than 60 characters. If the submission includes supplementary data (see below) indicate this on the title page and list the supplementary data items submitted.

Abstract

The second page of every manuscript must contain the structured Abstract, which should not exceed 250 words. The Abstract should include each of the following sections:
Objective: A brief statement of the purpose of the study
Method: A summary of the participants as well as descriptions of the study design, procedures, and specific key measures.
Results: A summary of the key findings, including specific results of significance testing to the extent that space allows
Conclusions: Clinical and theoretical implications of the findings as space allows.

Abbreviations and reference citations should be avoided.

Key words

Up to six key words, which will appear after the abstract, should be included below the title, each separated by a semicolon (;). Keywords should be selected from the APA list of index descriptors, unless otherwise agreed with the Editor. Thus, please give them careful consideration.

Funding

Details of all funding sources for the work in question should be given in a separate section entitled 'Funding'. This should appear before the 'Acknowledgements' section.
The following rules should be followed:

- The sentence should begin: 'This work was supported by …'
- The full official funding agency name should be given, i.e. 'National Institutes of Health', not 'NIH' (full RIN-approved list of UK funding agencies) Grant numbers should be given in brackets as follows: '[grant number xxxx]'
- Multiple grant numbers should be separated by a comma as follows: '[grant numbers xxxx, yyyy]'
- Agencies should be separated by a semi-colon (plus 'and' before the last funding agency)
- Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number 'to [author initials]'.

An example is given here: 'This work was supported by the National Institutes of Health [AA123456 to C.S., BB765432 to M.H.]; and the Alcohol & Education Research Council [hfygr667789].'

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Acknowledgments

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References

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and those in press (state the journal which has accepted them and enclose a copy of the manuscript) may be included. In the text, a reference should be cited by author and date. Not more than six authors may be cited per reference; if there are more than six authors, use et al in the in-text parenthetical citation.
At the end of the manuscript, the citations should be typed in alphabetical order, with the authors' surnames preceding initials. References should include, in the following order: authors' names, year, complete title of the article, journal title, volume number, inclusive page numbers, and (for books only) name and address of publisher. The name of the journal should be italicized and appear in full. References will appear in type as below:

- Cary, C. L., Woods, S. P., Rippeth, J. D., Heaton, R. K., & Grant, I. (2006). Prospective memory in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology*, 28, 536–548.
- Park, D. C. & Kidder, D. P. (1996). Prospective memory and medication adherence. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 369–390). Mahwah, NJ: Lawrence Erlbaum Associates Publishers.
- Lanktree, C., & Briere, J. (1991). Early data on the Trauma Symptom Checklist for Children. Paper presented at the meeting of the American Professional Society on the Abuse of Children, San Diego, CA.

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Appendix E: Protocol of original study

Working Protocol

Longitudinal Assessment of Short-term Memory Binding Functions in patients with Mild Cognitive Impairment

Dr Mario A Parra

Fellow of the Alzheimer's Society

Supporting Organizations

Alzheimer' Society, University of Edinburgh: HCN, CCACE, ASRC, and SDCRN

1. Introduction and Rationale

Carriers of the mutation E280A of the Presenilin-1 gene who will develop early-onset familial Alzheimer's disease (FAD) (Lopera et al., 1997) show progressive STM binding deficits throughout a long and otherwise asymptomatic period which starts around 15 years before they reach the age of onset of the disease (Parra et al., 2011; Parra et al., 2010). STM binding is not affected by other forms of non-AD dementia (Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012). We have proposed that STM binding is an early cognitive marker for AD.

The STM binding deficits observed in preclinical familial AD suggest that this function may be targeted by AD earlier than those assessed with traditional neuropsychological tasks. However, this is a genetic variant of AD (Holmes, 2002). We need to investigate whether this impairment also characterises patients who will develop late-onset sporadic AD such as those with Mild Cognitive Impairment (MCI). There is consensus that the amnestic form of MCI, either in its pure variant (only memory impairment - aMCI) or more remarkably in its mixed variant (multiple-domain amnestic MCI - mMCI), is that associated with the highest risk for conversion to AD.

In a recent cross-sectional study carried out in collaboration with the Department of Psychology of the Complutense University of Madrid, we piloted the STM task used in the earlier studies in FAD with a group of MCI patients. The initial results showed that the STM binding task effectively discriminated between controls and MCI patients. Out of 30 patients with MCI 20 showed below cut-off performance on the STM binding task. Interestingly, of the 20 MCI patients with mMCI 17 showed STM binding deficits whereas of the 10 patients with aMCI only 3 showed STM. These results suggest that STM binding deficits may inform on different risk levels for conversion to AD in patients with aMCI and in those with mMCI. Hence, these initial data suggest that this function is worth investigating longitudinally in these subtypes of MCI.

1.1 The present study

The present study aims to investigate STM binding longitudinally in patients with aMCI and mMCI. To this aim, a research protocol has been designed which comprises a set of novel and traditional neuropsychological tasks known to be useful in the early detection of AD. This protocol adheres to current guidelines for the early assessment of AD (Albert et al., 2011; Dubois et al., 2007; Winblad et al., 2004; Petersen, 2004a) and incorporates tasks which are claimed to be "cognitive markers" for this form of dementia. This methodology will permit the comparison of the sensitivity, specificity and predictive values across these different assessment methods. The outcomes of these analyses should inform on which of these tasks or combination of tasks would achieve a reliable prediction power.

2. Aims and Research Questions

To investigate whether STM binding deficits are present in patients with MCI and whether this impairment predicts conversion to AD.

1) Is STM binding a function sensitive to the preclinical stages of late-onset sporadic AD? Based on previous studies and on the results of our own pilot study, we hypothesize that a subgroup of MCI patients will show STM binding deficits. These patients will be those that will likely convert to AD.
2) Can the STM binding task achieve better classification and prediction power than other traditional Neuropsychological tasks and other recent cognitive markers for AD? Based on our earlier studies in healthy elderly and in different forms of dementia including AD, we predict that STM binding may help overcome some limitation which currently undermine the sensitivity and specificity of available tests for AD (e.g., sensitivity to the effects of age or to different forms of dementia).

3. Methods

3.1 - Sample and sample size calculation

A total of 120 MCI patients and 60 controls will be assessed longitudinally for three years.

Power calculation: was performed which incorporated (1) pilot data obtained from 23 MCI patients and 30 controls as well as from 14 mild AD patients all assessed with the STM binding task proposed here. In addition a wide search of the literature was performed to obtain three main variables: (1) average follow-up period within which changes could be observed using sensitive cognitive tasks (3 years, see Fleisher et al., 2007), (2) MCI to AD conversion rate (median = per annum 12%, 37.65% for a 3-year study), (3) attrition (14% for a 3-year follow up study). The results showed that for a desired power of 80%, a medium effect size (Cohen d = 0.5) and alpha set at 0.05, 80 MCI patients and 40 controls at baseline we would allow us to reach the study end-point with a number of converters which will permit reliable comparisons (~ 20). However, as this will be a longitudinal, multicentre, international project, we aim to recruit 120 MCI patients and 60 controls as to control for variability across labs and dropouts.

3.2 - Participant selection procedures

3.2.1 - Exclusion Criteria for both Groups

(1) Active psychiatric illness, alcohol/drug history (score on the **GDS > 5**; Yesavage et al., 1982)
(2) Cerebro-vascular disease (Hachinski Ischemia **Score > 4;** Hachinski et al., 1975)

Maximal score	18
Vascular range	7-18
Mixed range	5-6
Degenerative range	0-4

(3) Significant underlying medical and/or neurological conditions
(4) Visual impairment:
    a. Colour blindness (**more than 2 errors** in the Colour blindness test; Dvorine, 1963)
    b. Perceptual binding test (80% correct – 4 out of 5 trials should be correct; Parra, Abrahams, Logie, & Della, 2010, see description of the task below)
(5) MMSE < 24 (if ACE available, the MMSE is taken from ACE)

3.2.2 - Inclusion Criteria for MCI

MCI criteria as set by Petersen (2004) and Winblad et al. (2004)

(1) Change in cognition recognized by the affected individual **and/or** a close informant (as suggested by Morris, 2012; Storandt, Grant, Miller, & Morris, 2006)
    a) Have you (she/he) had any thinking or memory problems? ➔ Yes
    b) Has there been some decline in memory over the last year? ➔ Yes
    c) When did you first notice that your memory was not as it used to be? dd/mm/yy
    d) Everyday Cognition – ECog (Farias et al., 2008)
    * Memory should be (+)

    Greenaway, Duncan, Hanna, & Smith, (2012)

	MEAN	SD	SAMPLE RANGE	NORMAL RANGE
ECog				
Memory	20.1	6.0	8–32	8[1]
Language	14.2	4.9	9–30	9
Visuospatial	10.8	3.6	7–22	7
Exec Fx/planning	8.0	3.4	3–18	4
Exec Fx/organization	11.7	4.8	5–24	6
Exec Fx/divided attention	7.9	3.1	3–16	4

[1]Based on the score that would be obtained by selecting "no difficulty" on all items of that subscale. Scores lower than this in the current sample reflect a failure of the participant to answer every item.

(2) MMSE **≥ 24** (and/or ACE >= 80; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006)
(3) Objective memory impairment:
    a) ACE Score (Memory Domain (of 26): Age 60-69 **≤ 19**, 70-75 **≤ 17**; Mioshi et al. 2006)
    b) HVLT (HVLT–R delayed recall (of 12): Controls: 8.1 (2.7) = 5.4; aMCI: 4.65 (0.7) = 5.35). **Cut-off = ≤ 4** (< 1.5 SD of the norms; Lonie et al., 2010)
(4) Independence in functional activities (see a more detailed description below)

a) IADL (Lawton & Brody, 1969)- Completely Normal Score (**8 in women and ≥5 in men**)

(5) Absence of dementia (Jack, Jr. et al., 2011; McKhann et al., 2011; McKhann et al., 1984) according to the NINCDS- ADRDA criteria listed below:

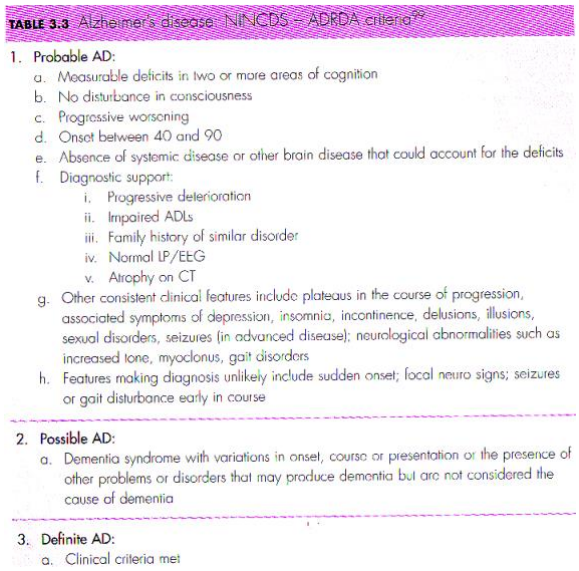


TABLE 3.3 Alzheimer's disease: NINCDS – ADRDA criteria[20]

1. Probable AD:
   a. Measurable deficits in two or more areas of cognition
   b. No disturbance in consciousness
   c. Progressive worsening
   d. Onset between 40 and 90
   e. Absence of systemic disease or other brain disease that could account for the deficits
   f. Diagnostic support:
      i. Progressive deterioration
      ii. Impaired ADLs
      iii. Family history of similar disorder
      iv. Normal LP/EEG
      v. Atrophy on CT
   g. Other consistent clinical features include plateaus in the course of progression, associated symptoms of depression, insomnia, incontinence, delusions, illusions, sexual disorders, seizures (in advanced disease); neurological abnormalities such as increased tone, myoclonus, gait disorders
   h. Features making diagnosis unlikely include sudden onset; focal neuro signs; seizures or gait disturbance early in course
2. Possible AD:
   a. Dementia syndrome with variations in onset, course or presentation or the presence of other problems or disorders that may produce dementia but are not considered the cause of dementia
3. Definite AD:
   a. Clinical criteria met

Figure 1. NINCDS- ADRDA criteria for AD (Taken from Burns & Morris, 2008)

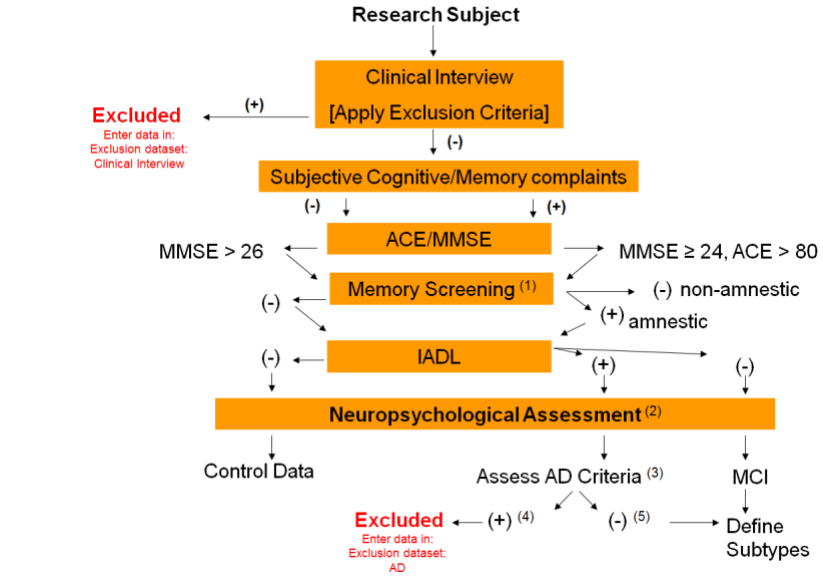
3.2.3 - Inclusion Criteria for Controls

Individuals who are cognitively, functionally, and neurologically intact:

(1) Free of memory and cognitive disorders (MMSE > 26)
(2) Live independently without difficulty (Normal Score on the scale of IADL and on ECog)

3.2.4 - Procedures for the participant selection process

All the referrals (i.e., controls and patients) will be treated as research subjects until the classification process sets in Figure 2 is undertaken. This process is aimed at accurately allocating individuals into the two groups: Controls and MCI. For such a purpose all the study subjects will be assessed with the same selection criteria.



(1) If ACE available, the Memory items will be used for screening purposes, alternative a standardized memory test should be used (e.g., RVLT, TAVEC)
(2) If IADL + only standard neuropsychological tasks are used to aid the decision making process (e.g., AD?) otherwise they will perform the entire protocol
(3) For example ADL +, impairments in multiple cognitive domains (< 2 SD), personal and family history, MRI or CT scan, other positive biomarkers.
(4) Patients will be excluded only at baseline. No AD patient will be recruited into the study. From second study point onwards they will enter the follow up.
(5) These patients will be coded as MCI with functional deficit: f_aMCI or f_mMCI and will be asked to perform the VSTM binding task to complete protocol
All the excluded cases should be fully documented and entered in the Exclusion dataset

Figure 2. Flowchart of actions for the enrolment and follow up process.

Each research subject will take part in a Clinical Interview during which the 5 Exclusions Criteria set in section 3.2.1 will be verified. A positive answer/score in **any** of them will exclude the subject. The 5 criteria should be verified even if the subject scored positive in one of them. The scores and a brief description of the clinical background will be entered in the Exclusion Dataset (sheet: Clinical Interview) to document the subject exclusion. If the subject volunteered as a control ***and*** the reason(s) for exclusion is (are) clinically meaningful ***and*** unknown by the subject, advice to approach the GP/Consultant should be provided (letter to the GP/Consultant – see Ethics).

If the research subjects successfully complete the Clinical Interview, they will be asked the three questions presented in section 3.2.2.1.a, b and c. The family member or the person accompanying the subject should complete the ECog scale. If no one can attend to the interview with the patient, this questionnaire should be posted to or complete over the telephone with the help of a relative before the appointment. This information should be available during the first interview.

In addition to the subjective memory assessment described above (3 questions + ECog questionnaire), an objective memory assessment will be performed (memory screening). For this, the score on the Memory Domain of the ACE-R, if available, and the score on a standard test of memory, especially a verbal learning test, will be considered. For this protocol we recommend The Hopkins Verbal Learning Test (HVLT), the California Verbal Learning test (CVLT), the Rey Auditory Verbal Learning Test (RVLT) or the TAVEC which is the Spanish version of the CVLT. These tests have all proved very sensitive to MCI (Fleisher et al., 2007; Lonie et al., 2010; Molinuevo et al., 2011; Tierney, Yao, Kiss, & McDowell, 2005; Greenaway et al., 2006). A measure of delayed recall will be used and the cut-off will be 1.5 SD below the local norms. In the case of the HVLT, which is the memory test we will used in the British population, the cut-off score is 4 (Lonie et al., 2010).

If the research subject scores in the risk band on the MMSE (24-26) ***and*** subjective cognitive impairment are recorded in the interview ***and*** no memory problems are identified both in the ECog ***and*** using the objective Memory Screening test (within 1.5 SD of the norms), this subject will not be classified as amnestic MCI. With the aid of the ECog, impairments in domains other than memory will be identified.

If the research subject scored in the risk band on the MMSE (24-26) ***and*** refers subjective cognitive deficits in the interview ***and*** memory impairments are identified using both the ECog ***and*** the objective Memory Screening test (< 1.5 SD of the norms) this subject will be classified as amnestic MCI.

For both amnestic and non-amnestic MCI the IADL scale will be then applied. If functional impairments in instrumental activities of daily living are found, the standard neuropsychological tests described above will be applied. These will be used to aid in the diagnosis of AD (see Fig 1). If AD criteria are met, the patient will be excluded from the Study. The scores and a brief description of the clinical background will be entered in the exclusion dataset (sheet: AD) to document the subject's exclusion. The subject will be advised to approach the GP/Consultant and a letter will be sent explaining the subject's profile. The present study will focus on MCI only. We will follow longitudinally subjects at risk for AD but who do not meet AD criteria at the time of the enrolment in the study. If functional impairments in instrumental activities of daily living are found but no AD criteria are met, the subject will perform the standard neuropsychological tests described below plus the novel STM binding task. The clinical phenotype of MCI will be then identified (non-amnestic MCI –nMCI-, amnestic MCI –aMCI, and multiple domain amnestic MCI – mMCI). If functional impairments are identified, the participant will be coded differently in the database (f_nMCI, f_aMCI or f_mMCI) highlighting that functional impairments were found at baseline. Following on from recent suggestions on the risk of permitting functional impairment in the diagnosis of MCI, we decided to control for this factor as to better distinguish between MCI and very early AD (Morris, 2012). If no functional impairments in

instrumental activities of daily living are found, the research subject will perform the standard neuropsychological tests described below plus the novel STM binding task.

If the research subject (1) scores above the risk band on the MMSE (> 26) ***and*** (2) does not refer subjective cognitive deficits in the interview ***and*** (3) no memory problems are identified with the ECog ***and*** (4) the Memory Screening test (within 1.5 SD of the norms) ***and*** (5) the IADL score is normal, this subject will be classified as a Control.

3.3 Neuropsychological Assessment

3.3.1 Standard Neuropsychological Tests

For the present study we have chosen standard tests of neuropsychological functions which have been found to hold high sensitivity and specificity for AD and also a good predictive value to assess conversion from MCI to AD. Some of these tests are recommended by current guidelines for the detection of preclinical AD (Albert et al., 2011; Dubois et al., 2007; Jack, Jr. et al., 2011).

3.3.1.1 Memory

a) Free and cued selective reminding test (Buschke et al., 1999; Grober, Buschke, Crystal, Bang, & Dresner, 1988; Buschke, 1984)
b) HVLT (CVLT, RVLT or TAVEC) (Benedict, Schretlen, Groninger, & Brandt, 1998)
c) Recall of Rey Figure (Osterrieth, 1944)
d) Digit Span

3.3.1.2 Visuo-spatial and constructional

a) Copy of Rey Figure (Osterrieth, 1944)
b) Clock Drawing (from ACE applying the criteria by (Shulman, 2000))
c) Visuo-Spatial Domain of ACE-R (Mioshi et al., 2006)

3.3.1.3 Attention

a) TMT_A (Reitan, 1958)
b) TMT_B (Reitan, 1958)

3.3.1.4 Executive Function

a) COWAT (Letter Fluency –FAS- and Animal Fluency from ACE-R) (Sumerall, Timmons, James, Ewing, & Oehlert, 1997)
b) TMT_B – TMT_A (Reitan, 1958)

3.3.1.5 Language

a) Graded Naming Test (Boston)
b) Language Domain of ACE-R (Mioshi et al., 2006)

3.3.1.6 Speed of processing and thinking

a) Digit to Symbol (Wechsler, 1997) (Letters and Numbers) (WM)

3.3.1.7 IQ

a) TOPF (Wechsler, 2012) – Replaced WTAR

3.3.1.8 Dementia Scale

a) CDR (Morris, 1993)
b) ACE-R (Mioshi et al., 2006)

3.4 STM Binding Paradigm

The STM binding paradigm comprises the Perceptual binding task used as an inclusion criterion and the STM binding task (polygons and colours (Parra et al., 2010; Parra et al., 2010)).

3.4.1 Perceptual Binding task

To explore perceptual binding a Visual Search Task is used. In this task participants are presented with two arrays of items on the computer screen. The screen is symmetrically divided in two halves by a black horizontal line. Two arrays of three coloured shapes are simultaneously presented in the upper and in the lower half. The first array shows and example of a "different trial" and will be used for practice purposes. There will then be 5 trials in the following order: [Same, Different, Different, Same, Different]. Arrays will be on the screen until the participants respond. The examiner will verify whether the response to each trial is correct or not. If 4 or more errors are committed, the examiner will repeat the 5 trials again. In order to be eligible to perform the Memory Binding task, participants should score above 80% accuracy in the perceptual task (4 out of 5 in a second presentation).

3.4.2 STM Binding task

This is a change detection task. Each trial presents two arrays, one study array followed by a test array. Arrays consist of 3 items presented in different locations between the study and test display (location is uninformative and should not be used as a memory cue). In 50% of the trials the two arrays are identical and in the other 50% two items in the test array change. The trial sequence is: a fixation cross presented for 500 ms followed by a study array presented for 2000 ms. This is followed by a blank retention interval of 1000 second after which the tests array is presented. The test array remains on until the participant has responded. Participants are asked to respond verbally by saying “same” or “different” depending on whether or not they detect a change between the study and test array. The examiner enters these responses using the keyboard. After the test display, a 5 point likert scale will ask participants to rate their confidence on the response emitted. There will be then a 1000 ms inter-trial interval.

Memory for shapes: In this condition participants will be presented with three shapes in black colour. Participants will be requested to remember these shapes. After the initial presentation they will decide whether the second screen consists of the same or different shapes. In different trials two new shapes will be replacing two shapes previously studied.

Memory for colours: In this condition participants will be presented with three different colours (the shape is the same within arrays hence shape is uninformative). Participants will be requested to remember these colours. After the initial presentation they will decide whether the second screen consists of the same or different colour. In different trials two new colours will be replacing two colours previously studied.

Memory for shape-colour binding: In this condition participants will be presented with three shapes each in a different colour. Participants will be requested to remember the combination of shapes and colours. After the study display they will decide whether the test display consists of the same or different combinations of shapes and colours. In the different trials shapes will swap colour. Because colours and shapes will be the same in the study and test display, it is required to remember what colour was with what shape during the study screen in order to detect differences across displays.

After the perceptual task, the participants will be presented with a practice session which will show 5 trials of the memory binding task. This is to allow participants to familiarise with the memory test. There is not requirement to pass this test, this is just a practice session. After this, participants will perform 32 trials of each conditions presented in a counterbalanced order.

3.4.1 Debriefing questionnaire to collect strategies

After the STM binding task participants will be asked about the strategies that they used to perform the task. These strategies will be collected using an structured questionnaire.

3.5 Procedure for the longitudinal assessment

There will be two assessment points after the baseline assessment. These will be carried out with an interval of 12 months (± 1 month). During each assessment point the participants (both controls and MCI patients) will undergo the same flow of actions presented in Figure 2. The only set of exclusion criteria for study points 2 and 3 are those used in the Clinical Interview, with the exception of point 2.2.1.(5). If the patients' IADL drop or they develop dementia during the study, this will be documented and they will continue in the study. Particularly, if the patients develop AD, the criteria which were met at that assessment point and on which the clinical decision was based will be documented in the dataset. If the patients' memory score improves of normalises from baseline, they will continue in the study. This change will be noted in the dataset. The entire protocol will be applied during each study point. Discontinued participants will be documented in the dataset. A brief summary of the reasons for discontinuation will be provided.

3.6 Statistical methods

Retrospective analysis will be carried out to adjust a linear model using logistic regression which will inform on the best predictors of MCI to AD conversion from baseline. Receiver Operating Characteristic Curves analysis will be performed to identify the sensitivity, specificity, positive and negative predictive values of the best predictors.

3.7 Auditing dataset

Two clinicians with experience in the diagnosis and assessment of dementia (a geriatrician and a clinical neuropsychologist) will independently audit the dataset to verify inconsistencies and to confirm the diagnosis.

4. Chronogram of actions

Ethics: July-August 2012

Extending Adoption SDCRN: August 2012

Baseline: Start September 2012

Study Point 2: Start September 2013

Study Point 2: Start September 2014

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6. Annexes

Task application

Perceptual task

"During this session, you will see some coloured shapes located above and below a black line. Your task is to say whether all of the coloured shapes that you see above the line are the same as the coloured shapes you will see below the line. If all of the coloured shapes that are above the line are the same as the coloured shapes below the line, you should say 'SAME'. If they are different, you should say 'DIFFERENT'. The location of these coloured shapes is not important. Just focus on the coloured shapes. You should try to do this as accurately and quickly as you can. Do you understand?"

If the examinee does not achieve a minimum of 4 out of the 5 trials, the memory task will not be applied. If the examinee does pass a minimum of 4 out of 5 trials, the test will proceed to the memory task.

Memory task

Shape only

Instructions for the participants

"In this part, you have to try to remember shapes. First of all, you will be shown three shapes. These will then disappear, and then you will be shown some new shapes. Your task is to say whether these new shapes are the same or different from the shapes you saw previously. If all of the shapes are the same, you should say 'SAME'. If there are different shapes you should say 'DIFFERENT'. The location of these shapes on the screen is not important. Just focus on the shapes. You should try to do this as accurately and quickly as you can. Do you understand?"

For each trial, press '2' if the examinee says 'Same', or press '1' if the examinee says 'Different'.

Colour only

Instructions for the participants

"In this part, you have to try to remember colours. First of all, you will be shown three colours. These will then disappear, and then you will be shown some new colours. Your task is to say whether these new colours are the same or different from the colours you saw previously. If all of the colours are the same, you should say 'SAME'. If there are different colours you should say 'DIFFERENT'. The

location of these colours on the screen is not important. Just focus on the colours . You should try to do this as accurately and quickly as you can. Do you understand?"

For each trial, press '2' if the examinee says 'Same', or press '1' if the examinee says 'Different'.

Shape-Colour Binding

Instructions for the participants

"In this part, you have to try to remember the coloured shapes. First of all, you will be shown three coloured shapes. These will then disappear, and then you will be shown some new coloured shapes. Your task is to say whether these new coloured shapes are the same or different from the coloured shapes you saw previously. You will decide whether all the combinations of shapes colours that you saw before are the same or different to the new combinations. If all of the coloured shapes are the same, you should say 'SAME'. If there are different coloured shapes to those you saw in the first display, you should say 'DIFFERENT'. The location of these coloured shapes on the screen is not important. Just focus on the coloured shapes. You should try to do this as accurately and quickly as you can. Do you understand?"

Appendix F: Ethics Approval Letter

Ethics Approval Letter CLIN782

SCHOOL *of* HEALTH IN SOCIAL SCIENCE

Edinburgh
Medical School
Doorway 6, Teviot Place

24 July 2020

Dear Caragh Maher

Application for Ethical Approval

Reference: CLIN782

Project Title: Predicting cognitive decline: the role of visual memory binding

Thank you for submitting the above research project for review by the School of Health in Social Science Research Ethics Committee (REC). I can confirm that the submission has been independently reviewed and was approved on 26th June 2020.

The standard conditions of this approval are:

I. Conduct the project strictly in accordance with the proposal submitted and granted ethics approval, including any amendments made to the proposal required by the REC.

II. Advise the REC (by email to ethics.hiss@ed.ac.uk) of any complaints or other issues in relation to the project which may warrant review of the ethical approval of the project.

III. Make submission for approval of amendments to the approved project before implementing such changes.

IV. Advise in writing if the project has been discontinued.

The School's Research Ethics Policy and further information and resources are available on the School's website.

You may now commence your project; we wish you the best of luck.

Yours sincerely,

Sanni Ahonen

Administrative Secretary